STEREOCHEMICAL DIVERSITY IN THE SUBSTRATE-CONTROLLED STEREOSELECTIVE ALDOL COUPLINGS OF CHIRAL REACTANTS

A Thesis Submitted to the

College of Graduate and Postdoctoral Studies

in Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

in the

Department of Chemistry

University of Saskatchewan

Saskatoon

by

SUSHITAL JANA

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CANADA

The Head
Department of Chemistry
University of Saskatchewan
110 Science Place
Saskatoon, SK S7N 5C9
CANADA

ACKNOWLEDGEMENTS

My sincere gratitude to my supervisor Dr. Dale Ward for giving me the opportunity to work with him and to be a part of his group. I am thankful to him from the bottom of my heart for his constant support and encouragement. Thank you for everything you taught me during my graduate (Ph.D.) program.

I would like to thank my advisory committee members: Dr. Soledade Pedras, Dr. Jens Müller and Dr. Nicholas Low for their valuable suggestions throughout my graduate studies. Thank you for providing useful feedback during my advisory committee meetings. I must thank my course instructors for teaching me different aspects of chemistry.

I would like to thank Department of Chemistry, University of Saskatchewan, and Natural Sciences and Engineering Research Council (NSERC) of Canada for their financial contribution. Thanks to the Saskatchewan Structural Science Center for providing the mass, NMR, and infrared facilities. Special thanks to Dr. Keith Brown, Dr. Jianfeng Zhu (Peter), and Dr. Ken Thomas.

Special acknowledgement to the TA managers: Dr. Marcelo Sales, Dr. Pia Wennek, and Dr. Alexandra Bartole-Scott for their support and assistance.

All my appreciation to Dr. Michel Gravel and his group for the beautiful moments and valuable discussion during joint group meetings.

I would like to thank all the past and present group members of the Ward group for their scientific contribution which directly or indirectly helped me to advance the chemistry I developed during my graduate (Ph.D.) program. Thanks to Dr. Mohammad Mehdi Zahedi (Pooyan), Dr. Fabiola Becerril-Jimenez, Muxi Cheng, Leon Lai, Thano Karagiannis, Mojtaba Biniaz, Diptarghya Kundu, Dylan McGill, Tram Truong, and Naveen Diddi for all their suggestions and for making the lab environment enjoyable.

I would like to thank my friends Venkat, Praveen, Mahesh, Bart, Heather, Baljit, Charles, Zayer, Nahid, Zahin, Zayed, Farhana, Sariar, Saiyara, Suzana, Sara, Sohail, Rabia, Afan, just to name a few, who have been a great support for me and my family during my stay in Saskatoon. My appreciation to every person who directly or indirectly helped me to complete my graduate (Ph.D.) study during last few years.

Most importantly, I am grateful to my family and relatives for their unconditional love and support. I must thank my father, Salil Ranjan Jana, my mother, Sumitra Jana, my father-in-law, Bikash Sarkar, and my mother-in-law, Kalpana Sarkar for believing on me and allowing me to pursue my carrier in Chemistry. I am thankful to my grandparents for their love and blessings.

I am thankful to my brothers (in-law): Utsa Jana, Kanchan Jana, Swapan Jana, Ashutosh Giri, Biplab Sarkar, and my sisters (in-law): Sheli Maal, Mitali Jana, Sabita Jana, and Bipasha Sarkar for their love and affection. Thank you to my nieces: Ayusmita Giri (Manti) and Shrestha Jana (Titli) with whom I did not get much time to spend yet.

My journey would not have been possible without Priya Sarkar Jana (wife), Shreyasi Jana (Sristi) (daughter) and Samriddhi Jana (Sanjh) (daughter) who always stood by me in both bad and good times. Thank you for believing in me.

Dedicated to

My Parents

(Salil Ranjan Jana & Sumitra Jana)

&

My Parents-In-Law

(Bikash Sarkar & Kalpana Sarkar)

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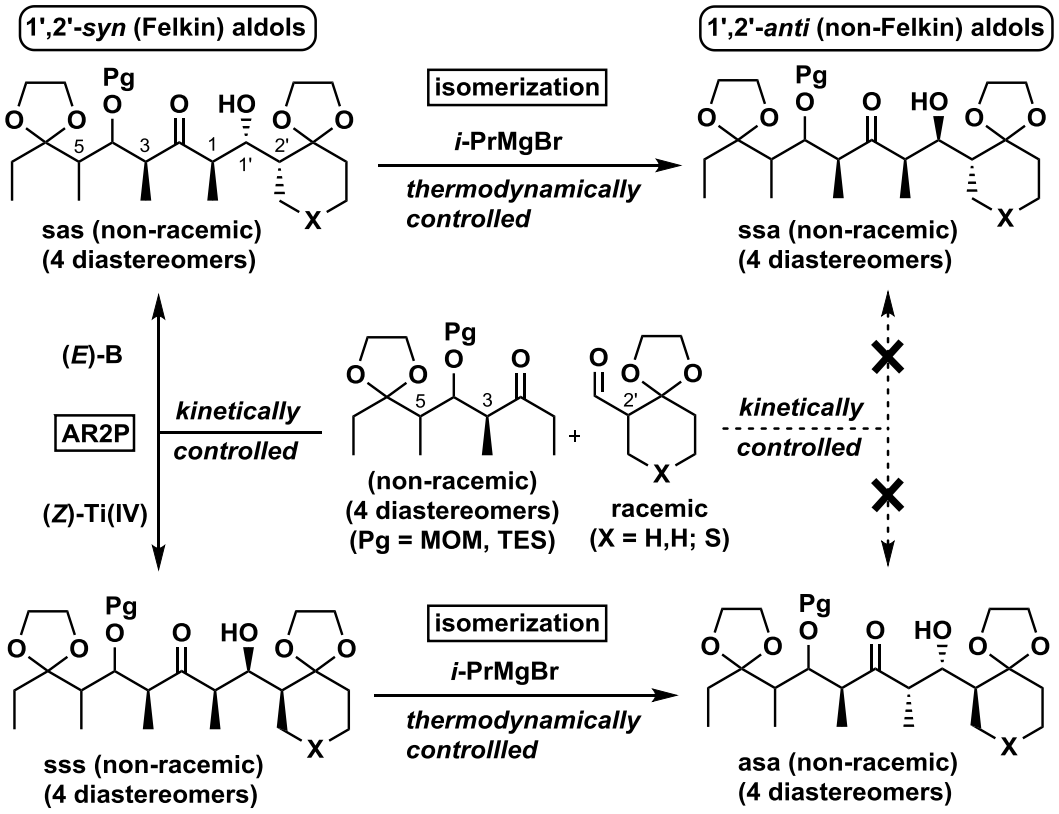
ABSTRACT

Undoubtedly, stereoselective aldol coupling is one of the most powerful tools available for synthetic chemists to effectively couple two non-racemic fragments in the late-stage of a total synthesis. Many successful applications of this strategy in polypropionate natural product syntheses have been reported. Notwithstanding these successful attempts, several examples have also been reported where the aldol coupling afforded undesired stereoisomers or resulted in surprisingly low diastereoselectivities. Consequently, either the route was no longer pursued (and a different disconnection approach was used) or the efficiency of the synthesis was compromised due to the low diastereoselectivities of the aldol couplings. Because the structure of the fragments to be coupled are dictated by the target molecule, significant changes of these structures would greatly influence the efficiency of the synthesis. A more cost-effective and practical solution to the aforementioned problems would require only simple modifications of the substrates (e.g., variation of protecting groups) or the reaction conditions (e.g., change in enolate type or geometry, temperatures) to alter the outcome of the reaction. Having a general approach toward polypropionates would overcome the aforementioned issues where most (if not all) of the possible diastereomers of an aldol coupling can be selectively accessed. Toward that end, the Ward group has designed aldol couplings that proceed with kinetic resolution (thiopyran route to polypropionates, TR2P) and accessed three (**aas**, **ass**, and **sas**) of the eight possible diastereomers (all Felkin) in their non-racemic form. This work also showed that with proper knowledge of each of the three stereocontrol elements (i.e., diastereoface selectivities of aldol additions to the ketone enol(ate) and aldehyde and the relative topicity of coupling), rational design of aldol couplings proceeding with kinetic resolution is possible.

The objective of my research was to access the remaining five of the eight possible diastereomers by extending the TR2P to acyclic ketones and thereby, increase the stereochemical diversity in the aldol couplings of chiral fragments. After identifying suitable substrates and reactions conditions (from the model reactions where one of the coupling fragments was achiral), aldol couplings of chiral aldehydes with enolates of chiral ketones were performed under those reaction conditions in which the diastereoface selectivities of the aldol additions were high with respect to each of the coupling fragments. Aldol couplings of (*E*)-enol borinates proceeded with excellent mutual kinetic enantioselections (MKEs) and provided **sas** (racemic) as the predominant

product. In contrast, the aldol couplings of Ti(IV) (*Z*)-enolates proceeded with good to moderate MKEs and provided **sss** (racemic) as the major product. Aldol couplings with non-racemic ketones (i.e., kinetic resolution) provided enantioenriched **sas** and **sss** aldol adducts. This developed methodology (i.e., acyclic route to polypropionates, AR2P) provided access to two aldol diastereomers **sas** and **sss** (both Felkin).



[AR2P: acyclic route to polypropionates]

All attempts to obtain the remaining four (non-Felkin) diastereomers under kinetically controlled reaction conditions failed. Serendipitously, isomerization of Mg(II) aldolates (prepared by reaction of aldol adducts with *i*-PrMgBr) under thermodynamic control provided access to two (**ssa** and **asa**) of the remaining four non-Felkin diastereomers in non-racemic form. Under optimized conditions, good yields and excellent product diastereoselectivities favoring the non-Felkin aldols were obtained with several substrates. The product distribution under thermodynamic control was found to be strongly dependent on the chelating ability of the aldehyde component of the aldol adduct.

In favorable cases, the combination of kinetically controlled aldol couplings (TR2P and AR2P) with the above isomerization process provided selective access to six of the eight possible diastereomers in their non-racemic form. These aldol adducts have numerous applications in polypropionate natural product syntheses. The increased stereochemical diversity should provide more flexibility in the retrosynthetic design of polypropionate natural products.

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LIST OF ABBREVIATIONS

α	observed optical rotation in degrees
$[\alpha]_D$	specific rotation at the sodium D line (expressed without units; implied actual units are: (deg·mL)/(g·dm))
Å	angstrom, 10^{-10} m
Ac	acetyl
AcOH	acetic acid
anhyd	anhydrous
anti	defines the relative configuration of two stereogenic centers on a chain. If the chain is illustrated in a planar zigzag conformation and the specified substituents of the two stereogenic centers are on opposite sides of the planar chain, the relative configuration is *anti*. In this thesis, the stereogenic centers are sp^3 carbon atoms along a carbon chain and have one hydrogen and one non-hydrogen ligand. The *anti* descriptor refers to the non-hydrogen ligands
AR2P	acyclic route to polypropionates
ap	apparent (when describing the multiplicity of a NMR signal; *cf*. actual)
atm	atmosphere(s) (as a measure of pressure)
aq	aqueous
9-BBN	9-borabicyclo[3.3.0]nonyl
Bn	benzyl ($PhCH_2$-)
br	broad (description of a spectral signal)
Bu, *n*-Bu	normal (primary) butyl
n-BuLi	*n*-butyllithium
t-Bu	tertiary butyl
t-BuOH	*tert*-butyl alcohol
°C	degrees Celsius (temperature)
cal	calorie(s) (unit of heat; 4.184 Joules)
COSY	correlation spectroscopy
CI	chemical ionization (in mass spectrometry)
^{13}C NMR	carbon 13 nuclear magnetic resonance

$(COCl)_2$	oxalyl chloride
convn	conversion
conc	concentration
δ	NMR chemical shift in parts per million downfield from TMS
d	day(s); doublet (spectral signal)
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
dil	dilute
DIPCl	chlorodiisopinocampheylborane
i-Pr_2NH	*N*,*N*-diisopropylamine
i-Pr_2NEt	ethyldiisopropylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomer ratio
ds	diastereoselectivity
DRIFT	diffuse reflectance infrared Fourier transform
E and *Z*	configurational descriptors for alkenes. *E* denotes that the substituents of highest CIP (Cahn-Ingold-Prelog) priority at each end of the double bond are on opposite sides. If the pertinent substituents are on the same side, the descriptor is *Z*
equiv	equivalent(s)
EtOAc	ethyl acetate
ee	enantiomeric excess
ent	enantiomer of
FAB	fast-atom bombardment
FCC	flash column chromatography
h	hour(s)

Hz	Hertz
c-Hex	cyclohexyl
HF	hydrofluoric acid
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
^{1}H NMR	proton nuclear magnetic resonance
HMBC	heteronuclear multiple bond correlation (a 2D NMR experiment)
HSQC	heteronuclear single quantum correlation (a 2D NMR experiment)
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared
ISOM	isomerization
IBX	2-iodoxybenzoic acid
J	coupling constant (in NMR spectroscopy)
K	Kelvin (absolute temperature in degrees)
k	kilo
KR	kinetic resolution
L	liter (s)
like	stereodescriptor denoting those stereoisomers of a set whereby two designated stereogenic centers have the same (*R* or *S*) absolute configuration
LiHMDS	lithium hexamethyldisilazide
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
m	multiplet (spectral), meter (s), milli
M	molar (moles per liter), mega
MHz	megaHertz
max	maximum
min	minimum, minute(s)

MKE	mutual kinetic enantioselection
mol	mole(s)
MOM	methoxy methyl (CH_3OCH_2-)
μ	micro
NaOMe	sodium methoxide
NBS	*N*-bromosuccinimide
nOe	nuclear Overhauser enhancement
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
Py	pyridine
PPTS	pyridinium *para*-toluene sulfonate
PTLC	preparative thin layer chromatography
q	quartet (spectral)
R*f*	retention factor
Raney Ni	Raney nickel
R and *S*	absolute stereochemical configuration descriptors in the CIP (Cahn-Ingold-Prelog) system
rt	room temperature (22-23 °C)
rac	racemic (also denoted by (±))
s	singlet (spectral), second(s)
sat	saturated
syn	defines the relative configuration of two stereogenic centers on a chain. If the chain is illustrated in a planar zigzag conformation and the specified substituents of the two stereogenic centers are on same sides of the planar chain, the relative configuration is *syn*. In this thesis, the stereogenic centers are sp^3 carbon atoms along a carbon chain and have one hydrogen and one non-hydrogen ligand. The *syn* descriptor refers to the non-hydrogen ligands

t	triplet (spectral)
temp	temperature
TES	triethylsilyl (Et_3Si-)
TMS	trimethylsilyl
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl (*t*-$BuMe_2Si$-)
TBSCl	*tert*-butyldimethylsilyl chloride
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TR2P	thiopyran route to polypropionates
TLC	thin layer chromatography
p-TsOH	*p*-toluenesulfonic acid
UV	ultraviolet

1. INTRODUCTION

1.1. Polypropionates

Polypropionates are an important subclass of a large family known as polyketides which are ubiquitous in nature. Polypropionates are characterized by the presence of a long carbon chain with alternating methyl and hydroxyl (or oxo) functionalities (e.g., **3**, Figure 1.1).[1] Polypropionates are the secondary metabolites found in bacteria, fungi, plants and animals. Their biosynthesis involves decarboxylative condensation between suitably activated propionate units such as **1** and **2**. The reaction is catalyzed by a family of enzymes or enzyme-complexes known as polyketide synthetases (PKS).[2-3] Natural products containing polypropionate motifs are often found to be biologically active and have a vast range of biological activities such as cytotoxicity, neurotoxicity, antifungal, antiviral, anticancer, and antiparasitic.

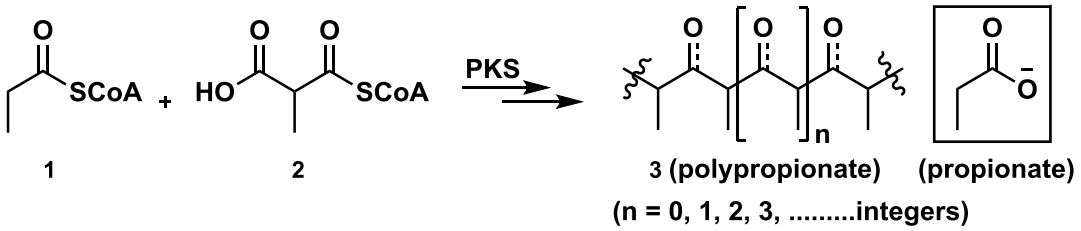


Figure 1.1. Biosyntheses of polypropionate motifs.

The structural and stereochemical complexities of polypropionates together with their diverse biological activities prompted synthetic chemists to develop methods for their stereoselective construction.[4-6] Several methods have been developed which involve stereoselective formation of a C-C bond including crotylation,[7-13] allylation,[14-19] Diels-Alder,[20-24] Claisen rearrangements,[25-26] Tischtchenko reaction,[17] alkylation followed by hydroxylation,[27] propargylation-reductive coupling,[28-29] hydroformylation,[30] formate reduction,[31] allenyl metal additions,[32-36] iodocarbonylations,[37] reiterative epoxide-based methodology,[38] and stereocontrolled lithiation–borylation reactions.[39] However, most of these methods require additional steps to install the methyl and(or) hydroxyl (or oxo) groups decorating the polypropionate backbone. Aldol coupling is one of the most powerful methods to construct

polypropionate motifs, stereoselectively. One of the main advantages of aldol coupling is that the product has the oxygen functionalities (hydroxyl and oxo) in the required 1,3-positions.

The aldol reaction involves addition of an enol equivalent to a carbonyl compound (e.g., aldehyde or ketone) to generate a β-hydroxy carbonyl product.[40] The products are referred to as 'aldol adducts' or simply 'aldols'. Traditionally, these reactions were carried out under protic conditions in which an enol or enolate (**6**) is formed transiently and reacts reversibly with an electrophilic carbonyl compound (**5**) (Figure 1.2).[41] Therefore, product formation for such C-C bond forming reactions is under thermodynamic control.

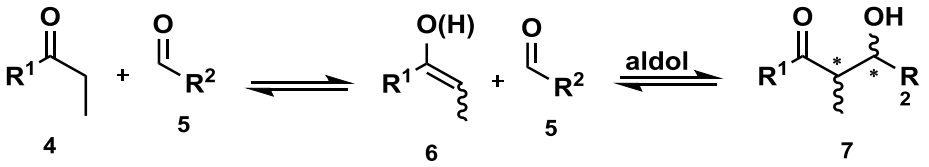


Figure 1.2. Traditional aldol reaction.

Due to the lower stability of the aldol adduct **7** compared to that of the starting materials (**4** and **5**), the equillibrium favors the starting materials **4** and **5** (Figure 1.2).[42] Additionally, the overall entropy change for the forward reaction is negative, making the formation of **7** unfavorable. The equilibrium is often displaced toward the product by dehydration or derivatization (e.g., β-cholorination, acylation, etc.) of **7** which limit its synthetic applications.[41] Moreover, the reaction becomes more complicated when the two reactants are not identical, resulting a complex mixture of self-aldol (between identical molecules) and cross/mixed aldol (between different molecules) adducts. Extensive investigation has been done for more than two decades to overcome the aforementioned challenges. The directed aldol coupling[43] evolved as the most effective and synthetically useful method. In the directed aldol coupling, the enolate **8** (M = B, Li, Mg, Sn, Ti) is generated quantitatively from **4** prior to introduction of the aldehyde **5** (Figure 1.3). The coupling between **8** and **5** is favored due to the formation of bidentate chelate **9b** at lower temperature in aprotic solvents.[42] The higher stability of chelate **9b** compared to that of **8** and **5** makes the aldol addition step irreversible. Finally, work up of the reaction provides the aldol adduct **7**.

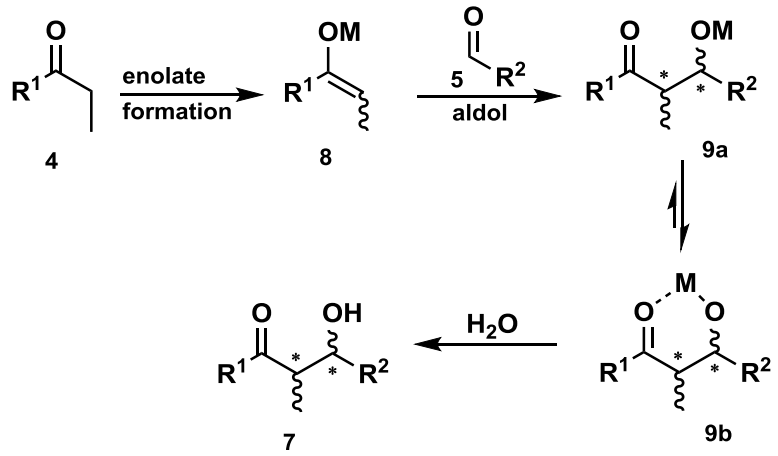


Figure 1.3. Directed aldol coupling reaction.

1.2. Stereocontrol elements in aldol coupling

Undoubtedly, the directed aldol coupling is one of the most powerful tools available in the arsenal of synthetic chemists for the stereoselective construction of a carbon-carbon (C-C) bond. Numerous applications[5, 44] of the directed aldol coupling[43] have been reported in polypropionate natural product syntheses where two chiral (non-racemic) fragments have been effectively coupled. In a directed aldol coupling of two chiral fragments proceeding under kinetic control, the diastereoselectivity of the reaction depends on three stereocontrol elements.[6, 45-49] Two of these stereochemical determinants are associated with the local chirality of the individual coupling fragments: namely, the diastereoface selectivities of aldol additions of the enolate and the aldehyde. The third determinant is the relative topicity of the coupling. Each of these stereocontrol elements and their effects are discussed in the following sections in the context of a directed aldol coupling.

1.2.1. Relative topicity in aldol coupling of achiral reactants

Directed aldol coupling between two achiral components can produce up to four stereoisomeric products. For instance, the enolate of ethyl ketone **4** can have both (*Z*)- and (*E*)-geometries (Figure 1.4). The (*Z*)-enolate **8a** has two π-faces (*re* and *si*; note that the enolate π-face is defined with respect to the C1 center) as does the aldehyde **5**. The coupling of **8a** and **5** can give up to four stereoisomeric products from the four different face-to-face reaction modes (*re*-*re*, *si*-*si*, *re*-*si*, and *si*-*re*). Similarly, the aldol coupling of (*E*)-enolate **8b** and **5** can form the same four

stereoisomeric products from the four different combinations of their π-faces. In a kinetically controlled aldol coupling, the preferred relative topicity (also known as simple diastereoselectivity[47]) can be evaluated from the product distribution of *like* (*re-re* and *si-si*) versus *unlike* (*re-si* and *si-re*) reaction modes. The relative topicities of the reactions shown in Figures 1.4 and 1.5 are the ratios of (**13a** + **14a**) and (**13s** + **14s**).

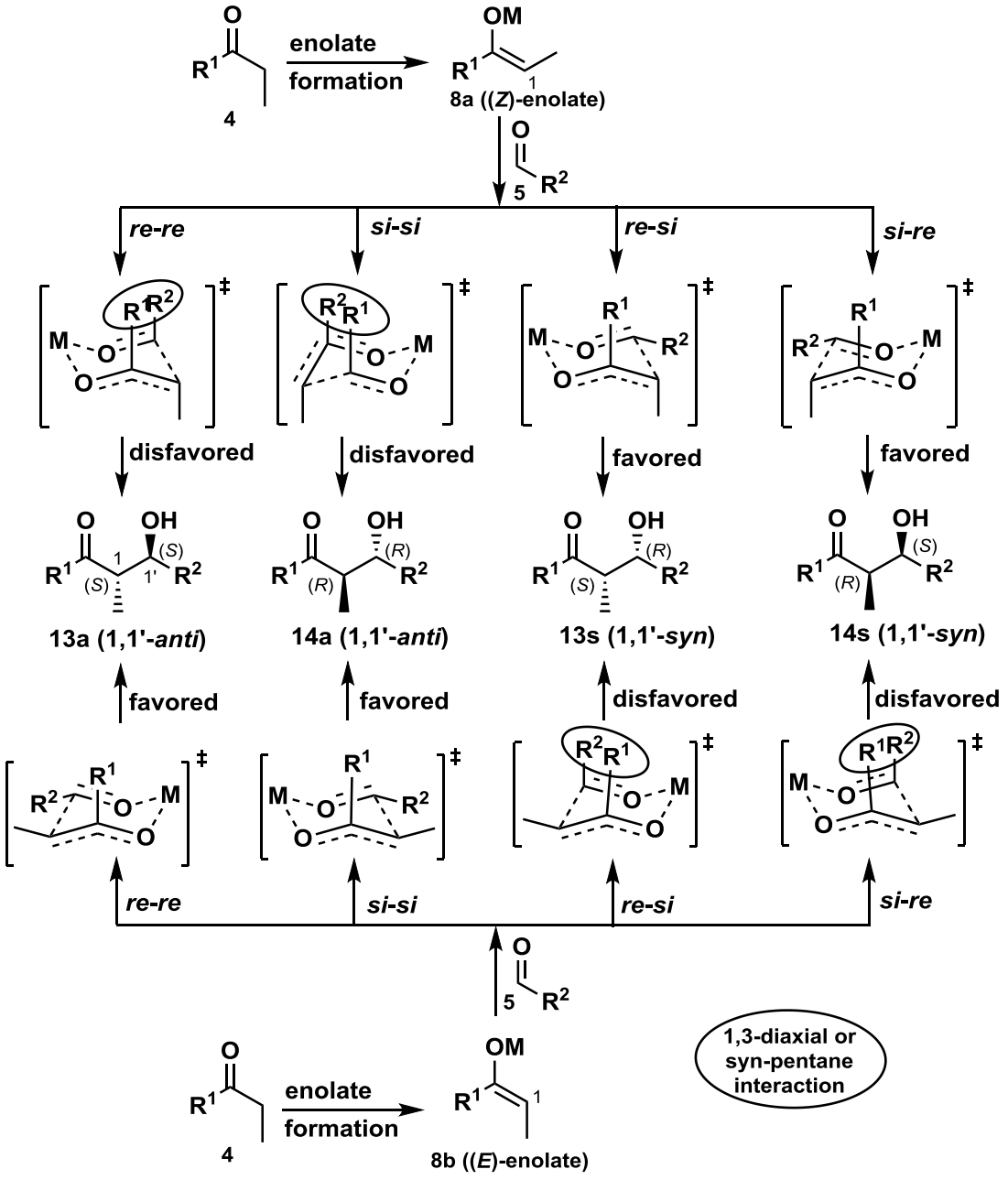


Figure 1.4. Zimmerman-Traxler (closed) transition state model (adapted from reference 1).

In the absence of a chiral environment, the transitions states from the *like* reactions (*re-re* and *si-si*) are enantiotopic and the corresponding products are enantiomers. Similarly, the products from the *unlike* reactions (*re-si* and *si-re*) are enantiomers. Hence, each of the enolates **8a** and **8b** can form up to two diastereomers (1,1′-*syn* and 1,1′-*anti*). The 1,1′-*syn* and 1,1′-*anti* relative configurations of the products are often directly correlated to the enolate geometry; that is, aldol coupling of the (*Z*)-enolate provides the 1,1′-*syn* adduct predominantly whereas the aldol coupling of the (*E*)-enolate provides the 1,1′-*anti* adduct, selectively. This correlation of the 1,1′-relative configuration to the enolate geometry is often rationalized by the Zimmerman-Traxler model[50] where the oxygen of the aldehyde group coordinates to the metal center of the enolate forming a closed pericyclic chair-like transition state (Figure 1.4). Products from transition states with minimal 1,3-diaxial interactions (also known as *syn*-pentane interactions) are preferred. It is well known in the literature that aldol additions of Li, Mg, B, Sn(II), and Ti(IV) enolates proceed via closed transition states where (*E*)-enolates provide 1,1′-*anti* and (*Z*)-enolates provide 1,1′-*syn* aldol adducts.[47-48] Therefore, stereoselective formation of the (*E*)- or (*Z*)-enolate is crucial to selectively obtain either 1,1′-*anti* or 1,1′-*syn* aldols.

In contrast to the above, addition of an enol silane (M = $SiMe_3$) to an aldehyde in the presence of a Lewis acid (LA) (known as Mukaiyama aldol[51]) proceeds without any coordination of aldehyde oxygen to the metal center (open transition state).[47] Diastereoselectivities of Mukaiyama aldol reactions are often predicted by an open transition state model where the aldehyde group and the enol silane are in an antiperiplanar orientation (Figure 1.5).[52] Products from transition states with minimal gauche interactions are favored. Unlike the aldol couplings of Li, Mg, B, Sn(II), and Ti(IV) enolates, there is no direct correlation between the geometry (*E* or *Z*) of the enol silane and the 1,1′-relative configuration of the product in Mukaiyama aldol coupling. In most cases, especially when R^1 and R^2 are bulky, 1,1′-*syn* aldols are preferred irrespective of the geometry of the enol silane.[53] Once again, in the absence of a chiral environment, products from *like* combinations (*re-re* and *si-si*) are enantiomers as are the products from *unlike* combinations (*re-si* and *si-re*). Consequently, two diastereomers are possible from the aldol coupling of **5** with **8**.

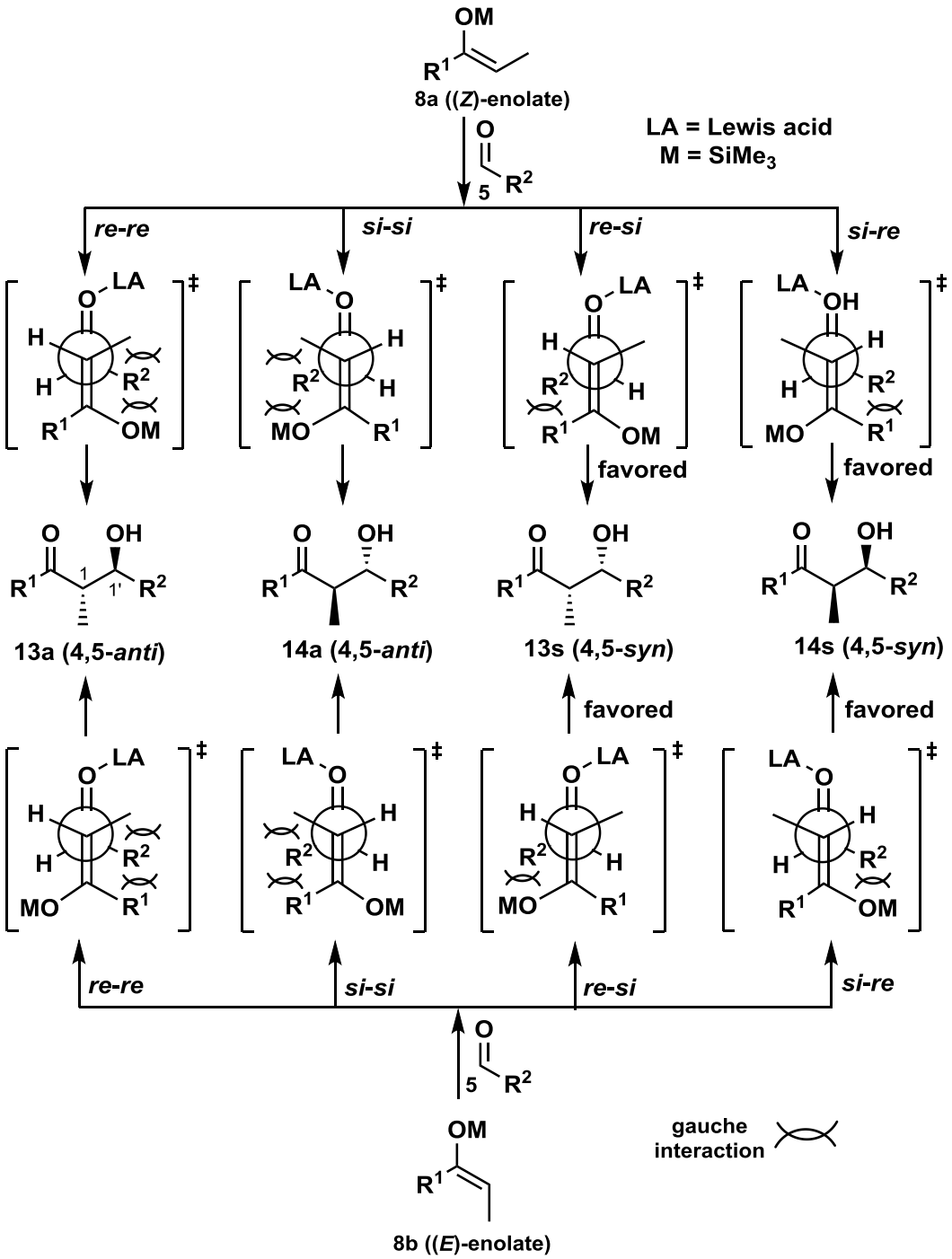


Figure 1.5. Open transition state model (M = $SiMe_3$) (adapted from reference 1).

In a chiral environment, each of the transition states shown in Figures 1.4-1.5 would be diastereomeric and unequal mixtures of aldol products would be expected. Examples of such an approach where two achiral fragments are coupled via directed aldol coupling in the presence of a chiral non-racemic reagent[54] or catalyst[55-58] have been reported in the literature and the products

were obtained in enantiomerically enriched form. Use of a chiral non-racemic auxiliary to couple two achiral substrates have also been reported[59-62] in the literature. Among the different auxiliaries reported, Evans' auxiliary (oxazolidinone **15**) is the most useful one as evident by its numerous applications[63-67] in polypropionate natural product syntheses. Different variations of Evans' auxiliary (e.g., oxazolidinethione and thiazolidinethione) have also been reported[68] in the literature.

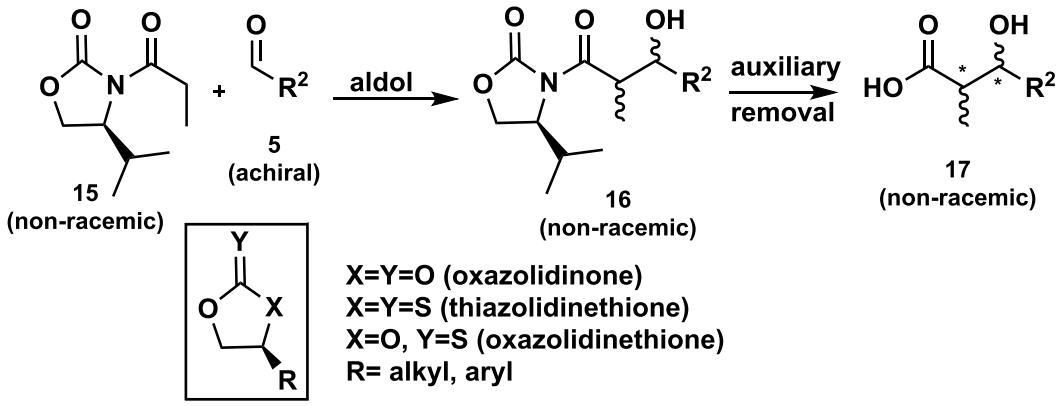


Figure 1.6. Evans' (type) chiral auxiliary in aldol couplings of achiral fragments.

The main disadvantage of the auxiliary approach is the incorporation and removal of the auxiliary that introduces additional steps in the synthesis and decreases its overall efficiency. The use of an auxiliary can be avoided by performing a substrate- controlled stereoselective aldol coupling.* The transition states shown in Figures 1.4 and 1.5 become diastereotopic when one of the reactants is chiral. For example, if the ethyl ketone **7** or the aldehyde **8** is chiral (*cf*. Figures 1.4 and 1.5) then the two π-faces are diastereotopic. Consequently, addition to one of the π-faces is faster than the other and one diastereomer is formed preferentially. In an aldol coupling, the preferential addition to one of the π-faces of a chiral reactant is referred to as the diastereoface or diastereofacial selectivity.[69] In the absence of non-linear effects[1, 70] the reaction between a chiral and achiral fragments would have the same diastereoselectivity irrespective of whether the chiral

* Although, the auxiliary approach can also be viewed as substrate controlled, in this thesis, the substrate-controlled stereoselective aldol coupling is strictly referred to the aldol couplings of substrates which do not possess any removable auxiliary.

reactant is racemic or non-racemic. The enantiopurity of the product diastereomers depends on the enantiopurity of the chiral reactant. The preferred diastereoface selectivity of chiral reactants in an aldol coupling can be evaluated from a simpler model reaction where one of the reactants is achiral.[71] For example, the preferred diastereoface selectivity of addition of an enolate (derived from a chiral ketone) addition to an aldehyde can be evaluated from the reaction with an achiral aldehyde. Similarly, the preferred diastereoface selectivity of enolate addition to a chiral aldehyde can be evaluated from the reaction with an achiral enolate. The following sections describe how the diastereoface selectivities of a chiral ketone and a chiral aldehyde can be evaluated from an aldol coupling with an achiral reactant.

1.2.2. Diastereoface selectivity of enolate addition to chiral aldehyde

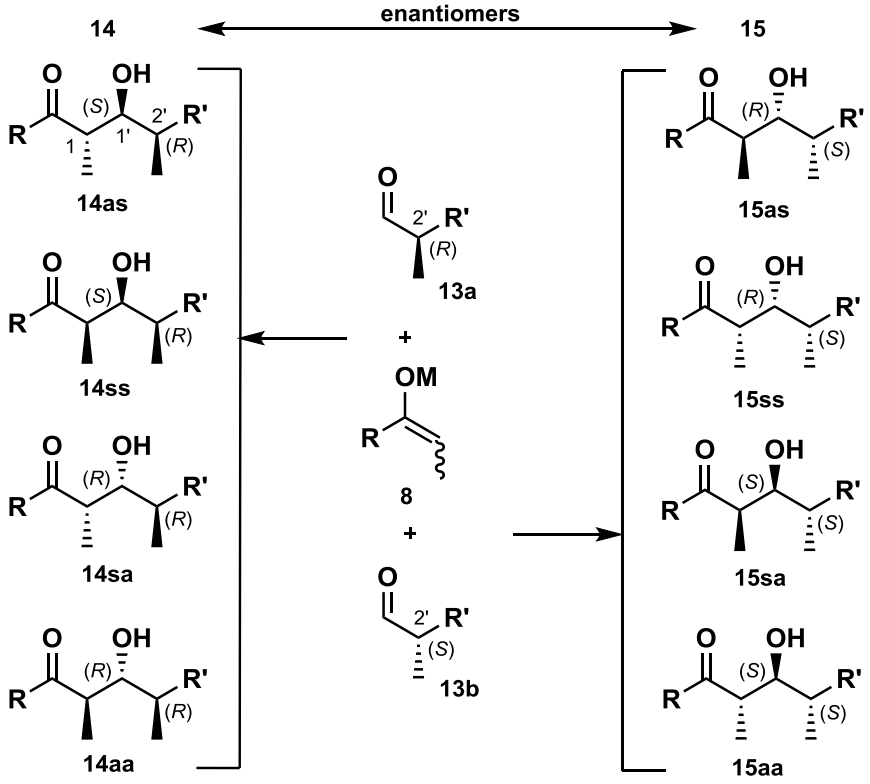


Figure 1.7. Aldol coupling of achiral enolate **8** with chiral aldehyde **13**.

The aldol coupling of an achiral enolate with a chiral aldehyde can give up to four diastereomeric products resulting from the four possible diastereomeric combinations of the π-faces (*re-re, si-si*, *re-si*, and *si-re*) of the reactants. For instance, the aldol coupling of **13a** and **8**

can form up to four diastereomers **14as**, **14ss**, **14sa**, and **14aa** (Figure 1.7).* Similarly, the aldol coupling of **13b** and **8** can also form up to four diastereomers **15as**, **15ss**, **15sa**, and **15aa**. Each of the four possible aldol adducts of **13a** is an enantiomer of one of the four possible aldol adducts of **13b**. Aldols **14as**, **14ss**, **15as**, and **15ss** with 1′,2′-*syn* relative configurations are referred to as Felkin aldols whereas aldols **14sa**, **14aa**, **15sa**, and **15aa** with 1′,2′-*anti* relative configurations are referred to as non-Felkin aldols. The relative configuration of C-1 and C-1′ stereocenters (i.e., relative topicity) is dictated by the enolate geometry (*cf*. Figure 1.4). Reaction of **(±)-13** (where both **13a** and **13b** are present), all eight possible stereoisomers will be formed as four diastereomers in racemic form. The diastereoselectivity of the aldol addition of achiral enolate **8** and **13a** or **13b** or **(±)-13** would be identical because each of the transition states leading to **14as**, **14ss**, **14sa**, and **14aa** are enantiotopic with one of the four transition states leading to **15as**, **15ss**, **15sa**, and **15aa**. In a kinetically controlled aldol coupling, the preferred diastereoface selectivity of addition of **8** to **13** can be evaluated from the ratio of 1,1′-*syn* (Felkin) to 1,1′-*anti* (non-Felkin) aldols — that is (**as**+**ss**) / (**sa**+**aa**).

* The lower case letters associated with the numerical label of each aldol adduct refers to the relative configurations of C3,C1 (if present), C1,C1′, and C1′,C2′ (if present) stereocenters, respectively where "s" stands for "*syn*" and "a" stands for "*anti*". For instance, aldol **14as** (does not have a C3 stereocenter) represents the diastereomer **14** which has 1,1′-*anti* (a) and 1′,2′-*syn* (s) relative configurations. The same convention is followed from here onwards for the labelling of the remaining aldol adducts presented in this thesis.

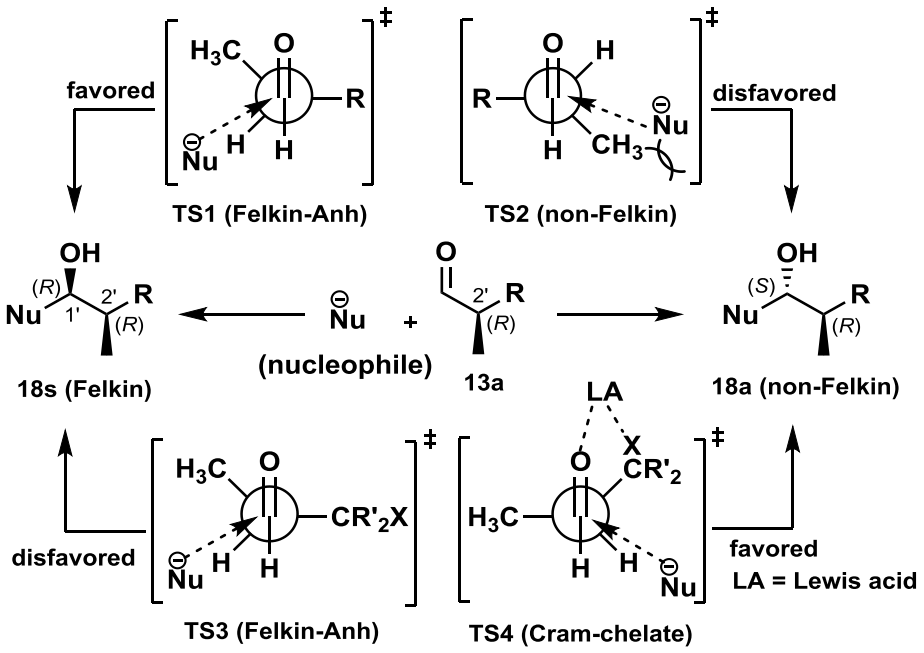


Figure 1.8. Felkin-Anh and Cram-chelate transition state models (adapted from reference 1).

Kinetically controlled nucleophilic additions to aldehydes where C-2′ is a stereocenter has been extensively investigated.[47-48, 72-73] The outcome can be rationalized and often predicted by various transition state models. For example, in the absence of chelation, the Felkin-Anh model[74-75] has been widely used to explain the outcome of a nucleophilic addition to a C-2′ substituted aldehyde. In contrast, the Cram-Chelate model[76-77] has been used to rationalize the outcome of a nucleophilic addition to an aldehyde with possible chelation from C-2′ or C-3′ stereocenter. For instance, the nucleophilic addition to **13a** can form two diastereomers, **18a** and **18s** (Figure 1.8). In the absence of a chelating effect, **18s** is the expected major product as predicted by the Felkin-Anh model. The main controlling factor in the Felkin-Anh model is the minimization of developing torsional strain as the geometry of the carbonyl carbon changes from trigonal to tetrahedral and the non-bonded interactions between the approaching nucleophile and the C-2′ substituent. According to the Felkin-Anh model the most reactive conformation of aldehyde **13a** is the one where the larger substituent "R" is oriented perpendicular to the carbonyl plane. The nucleophile approaches the carbonyl carbon center at an angle that is typically 105°± 5°. This specific angle of approach of the nucleophile to the carbonyl carbon center is known as the Bürgi-Dunitz trajectory.[78] To avoid steric repulsion, the nucleophilic attack occurs preferably from the side of the smallest group (H in **TS1**) over the medium group (CH_3 in **TS2**). Therefore, the

transition state **TS1** with minimal torsional strain is favored, leading to the formation of 1′,2′-*syn* (Felkin) aldol **18s** as the major product and the addition is Felkin selective. The minor product **18a** results from the unfavorable attack of the nucleophile from the side of methyl group (**TS2**). In the presence of chelation, **TS4** becomes the most reactive conformer, leading the preferential attack on to the opposite π-face (**TS4** versus **TS3**) of the aldehyde. Preferential attack of the nucleophile from the side of the smaller group (H in **TS4**) leads to the formation of 1′,2′-*anti* (non-Felkin) aldol **18a** as the predominant product. These models clearly suggest that the diastereoface selectivity of enolate addition to an aldehyde with C-2′ stereocenter strongly depends on the reaction conditions. The addition is expected to be 1′,2′-*syn* (Felkin) selective in the absence of chelation and 1′,2′-*anti* (non-Felkin) selective when chelation is favorable.

1.2.3. Diastereoface selectivity of aldehyde addition to chiral enolate

The two π-faces of an achiral enolate are enantiotopic in an achiral environment and diastereotopic in a chiral environment. In contrast, the two π-faces of a chiral enolate are necessarily diastereotopic irrespective of whether the environment is chiral or achiral. Thus, reaction of an enolate of a chiral ketone with an achiral aldehyde can form up to four diastereomeric products. As illustrated in Figure 1.9, the reaction of chiral enolate **19a** with achiral aldehyde **5** can form up to four possible diastereomers **23as**, **23ss**, **23sa**, and **23aa**. The 1,3-relative configuration of the aldol adduct is strongly influenced by the C-3 stereocenter present in **19a**. The 1,1′-relative configuration of aldol adduct is dictated by the enolate geometry (*cf*. Figure 1.4).

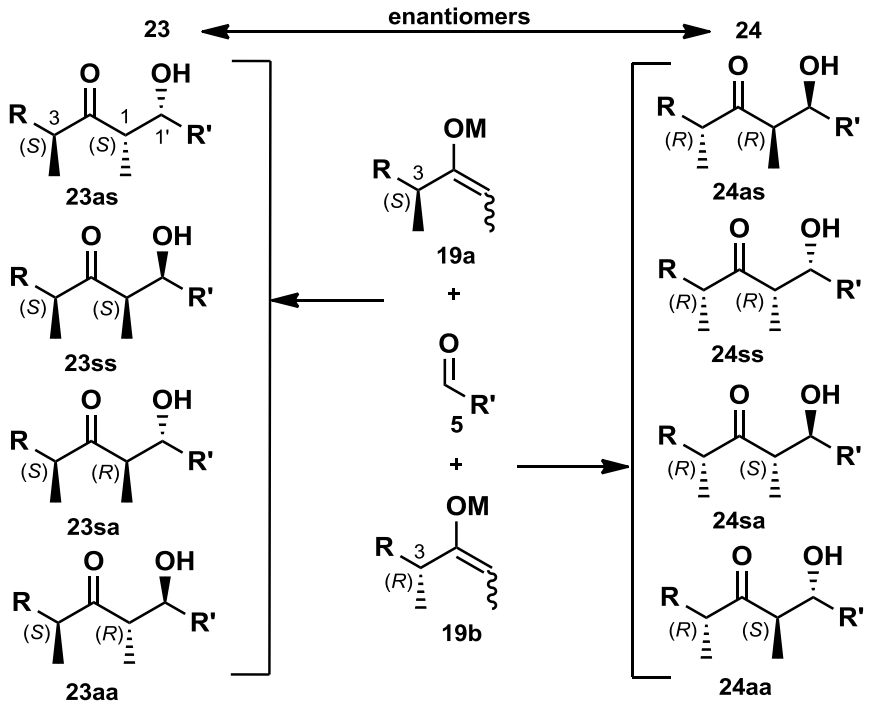


Figure 1.9. Aldol coupling of chiral enolate **19** with achiral aldehyde **5**.

The aldol coupling of **19b** (enantiomer of **19a**) and **5** can also lead to the formation of four diastereomeric products **24as**, **24ss**, **24sa**, and **24aa** which are enantiomers of **23as**, **23ss**, **23sa**, and **23aa**, respectively (Figure 1.9). Therefore, the aldol coupling of **5** with **(±)-19** (where both **19a** and **19b** are present) would lead to the formation of same four diastereomers **23** or **24** as a racemic mixture. The diastereoface selectivity of addition of **5** to **19a** or **19b** or **(±)-19** would be identical because each of the four transition states leading to **23as**, **23ss**, **23sa**, and **23aa** are enantiotopic with one of the four possible transition states leading to **24as**, **24ss**, **24sa**, and **24aa**. In a kinetically controlled aldol addition, the preferred diastereoface selectivity of addition of **5** to **19** can be estimated from the ratio of the sum of 1,3-*syn* aldol adducts to the sum of 1,3-*anti* aldol adducts — that is (**sa**+**ss**) / (**as**+**aa**).

The diastereoface selectivity of such an aldol coupling is often rationalized and predicted by considering the lowest energy conformers of the enolates based on preferred torsion angle of the C2-C3 bond (Figure 1.10). This torsion angle is strongly influenced by the allylic 1,3-strain ($A^{1,3}$).[79] The lowest energy conformer of (*E*)-enolate **19a** is **27a** with minimized $A^{1,3}$ strain where the H_3C at C1 and H at C-3 are eclipsed, orienting CH_3 and R substituents at C-3 above and below the H-C3-C=C plane. Thus, the *si* face of the enolate **27a** becomes most reactive and the

nucleophilic attack to **5** occurs from the less hindered face (i.e., side of CH_3 group at C-3), providing 1,3-*syn* diastereomer **23sa** as the predominant product. A less favorable attack from the more hindered face (i.e., side of R group at C-3) would result in formation of 1,3-*anti* diastereomer **23aa**. The 1,1′-*anti* relative configurations of **23sa** and **23aa** correlate to the (*E*)-geometry of the enolate (*cf*. Figure 1.4).

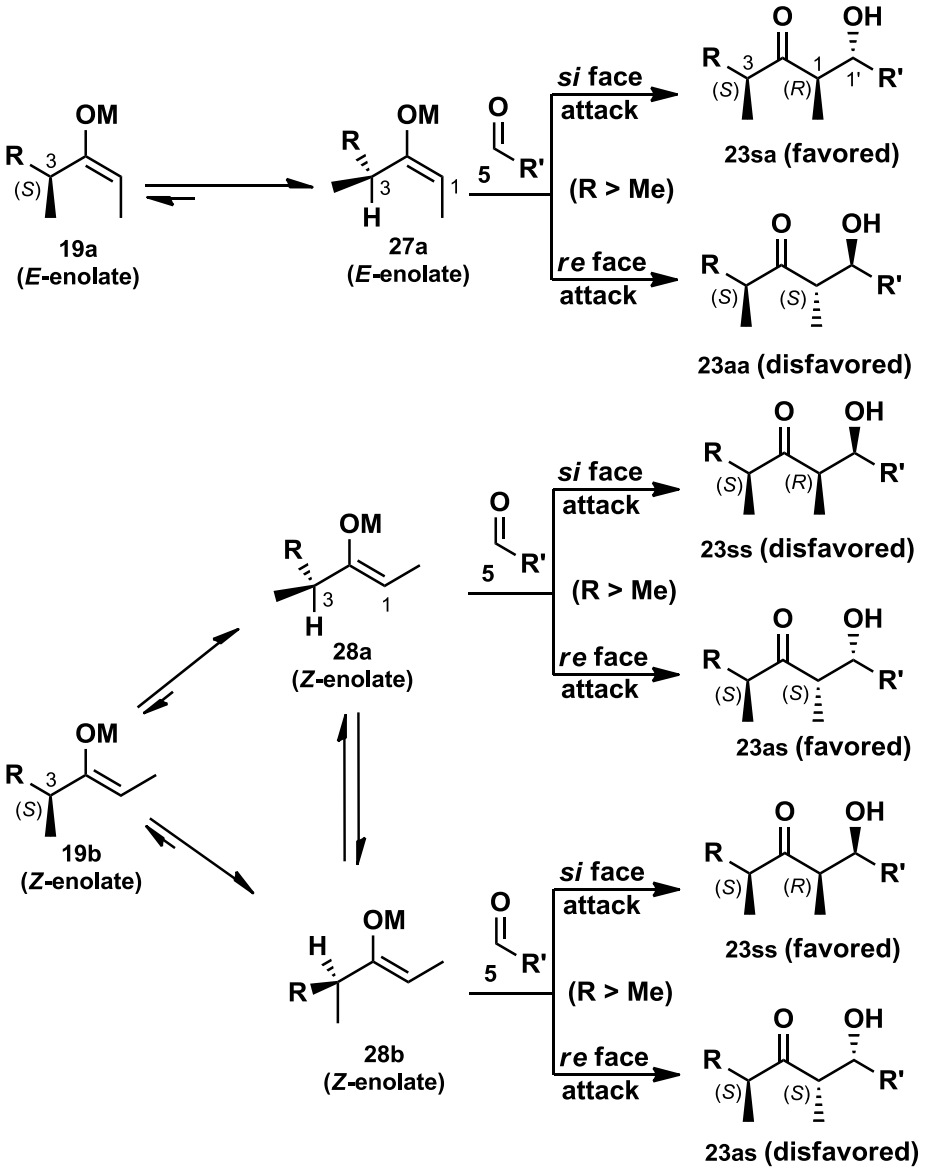


Figure 1.10. $A^{1,3}$ strain model for addition to enolates with C-3 stereocenter (adapted from reference 1).

Similar to (*E*)-enolate **19a**, the lowest energy conformer of (*Z*)-enolate **19b** is **28a** where H′s at C-1 and C-3 are eclipsed, orienting the CH_3 and R group at C-3 above and below the H-C3-C=C plane. Because of the (*Z*)-enolate geometry, the *re* face of **28a** (*cf*. *si* face of **27a**) becomes more reactive, providing the 1,3-*anti* diastereomer **23as** as the major product. The alternate conformer **28b** with H_3C at C-3 eclipsing with H at C-1 is only slightly higher in energy (ca. 0.7 kcal/mol).[79] Conformer **28b** has the R group and H above and below the H_3C-C3-C=C plane. Thus, the *si* face of **28b** (i.e., side of H) would be more reactive than either of the two faces of **28a** providing 1,3-*syn* diastereomer **23ss** as the predominant product.[1] The 1,1′-*syn* relative configuration of **23ss** and **23as** correlated to the (*Z*)-enolate geometry of **19b** (*cf*. Figure 1.4). The following section concerns how the diastereoface selectivity of aldehyde addition to an enolate of a chiral ketone changes with respect to protecting groups, enolate type and geometries in the context of aldol addition with an achiral aldehyde.

1.3. Multiplicativity rule

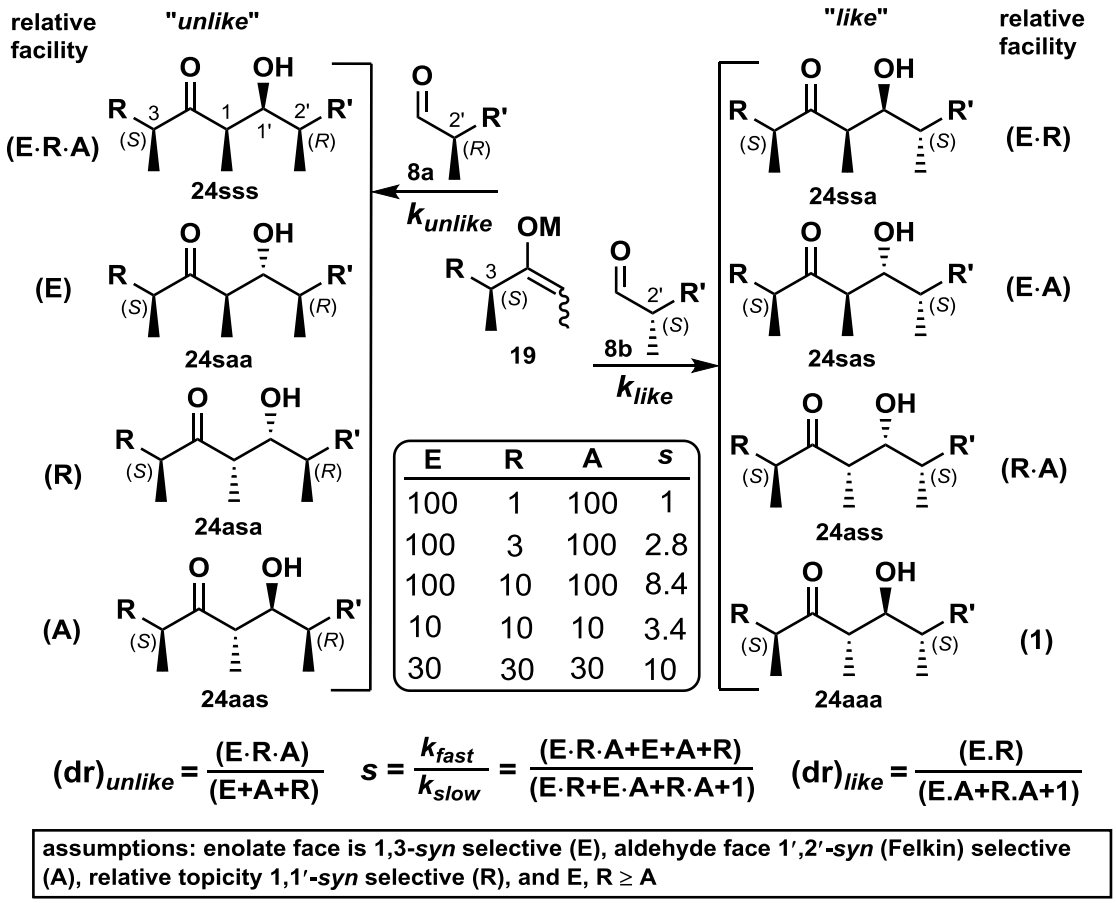


Figure 1.11. Application of the multiplicativity rule to the aldol coupling of **19** with **8** (adapted from references 1 and 84).

As illustrated in Figure 1.11 and discussed in references 1 and 84, aldol coupling of an enantiopure enolate (**19**) and an enantiopure aldehyde (**8a**) can form up to four possible diastereomers (**24sss**, **24saa**, **24asa**, and **24aas**). If one or both reactants are racemic (or simply not enantiopure), the coupling can lead up to eight diastereomers: four each from the *like* (with **8a)** and the *unlike* (with **8b**) combinations of the reactant enantiomers.* The terms *like* (the same configurations) and *unlike* (the opposite configurations) were originally proposed by Seebach and

* The terms *like* (same configurations) and *unlike* (opposite configurations) are defined with respect to the absolute configurations of the C-3 stereocenter of **19** and C-2′ stereocenter of **8**.

Prelog[80] to differentiate possible modes of reactions of chiral reactants. According to the multiplicativity rule, the kinetic stereoselectivity of such an aldol coupling can be factorized into three stereocontrol elements — the diastereoface selectivity of enolate addition to chiral aldehyde (**A**, refers to the relative propensity for the addition to one of the two π-faces (*re* or *si*) of the aldehyde and often designated by the 1′,2′-relative configurations (*syn* or *anti*) of the resulting product), the diastereoface selectivity of aldehyde addition to chiral enolate (**E**, refers to the relative propensity for the addition to one of the two π-faces (*re* or *si*) of the enolate and often designated by the 1,3-relative configurations (*syn* or *anti*) of the resulting product) and the relative topicity of their coupling (**R**, refers to the relative propensity for the addition of the *like* (*re*-*re*, *si*-*si*) versus *unlike* (*re*-*si*, *si*-*re*) π-faces of the reactants and often designated by the 1,1′-relative configurations (*syn* or *anti*) of the resulting product). The magnitudes of **A** and **E** can be estimated from the results of simpler model reactions where one of the reactants is achiral. The magnitude of **R** can be evaluated from the aldol couplings of achiral reactants (Figure 1.4) or from the aldol couplings of one chiral and one achiral reactant (*cf*. Figures 1.7 or 1.9). As described by Ward:[1]

"*Inspection of the structure of each of the eight possible aldol adducts in (Figure 1.11) clearly identifies the stereoselectivity of its formation with respect to the three stereocontrol elements (**E**: 1,3-syn/anti, **R**: 1,1'-syn/anti, and **A**: 1',2'-syn/anti). Assuming the biases of the stereocontrol elements are known, the relative facilities (i.e., rates) for the formation of the possible adducts are given by the product of the selectivities of those stereocontrol elements that have been satisfied in the formation of each adduct*."

For example and as illustrated in Figure 1.11, if **E** is 1,3-*syn* selective, **R** is 1,1′-*syn* selective and **A** is 1′,2′-*syn* selective then according to the multiplicativity rule, the coupling of **19** with **8a** (*unlike* reaction) is predicted to be selective in favor of **24sss** with a diastereoselectivity [i.e., **24sss** / (**24saa** + **24asa** + **24aas**)] equal to (**E**·**R**·**A**) / (**E**+**R**+**A**). This is the so-called "matched" reaction because the preferred relative topicity is complementary to the preferred diastereoface selectivities of **19** and **8a**. In contrast, the coupling of **19** with **8b** (*like* reaction) is "mismatched" because the preferred relative topicity is not complementary to the preferred diastereoface selectivities of **19** with **8b**. For example, the major product **24ssa** (assuming **E**, **R** ≥ **A**) is predicted to form with a diastereoselectivity [i.e., **24ssa** / (**24sas** + **24ass** + **24aaa**)] equal to (**E**·**R**) / (**E**·**A** + **R**·**A** + 1). In the "matched" reaction (*unlike* in Figure 1.11), one of the four possible

aldol adducts satisfies all three stereocontrol elements. In contrast, none of the four possible aldol adducts in the "mismatched" reaction (*like* in Figure 1.11) satisfies all three stereocontrol elements. Therefore, the predicted diastereoselectivity for the "mismatched" reaction is lower than that for the "matched" reaction. The enhanced diastereoselectivity for the "matched" reaction is referred to as double stereodifferentiation (DS).[69] As described by Ward:[1]

"*Each of the three stereocontrol elements has two possible biases resulting in eight possible combinations. For each combination, one of the diastereomeric adducts (in Figure 1.11) uniquely satisfies all three individual biases. This adduct should be the major diastereomer produced in the "matched" reaction. Regardless of whether the "matched" reaction is like or unlike, the multiplicativity rule-predicted diastereoselectivities for the "matched" and "mismatched" reactions are as illustrated in Figure 1.11. Inspection of these predictions suggests that all three stereocontrol elements must be reasonably highly biased for the diastereoselectivity of the "matched" reaction to be enhanced relative to the selectivity of the most selective element*."

The multiplicativity rule can be extended to predict the relative rates of the "matched" and "mismatched" reactions; i.e., k_{fast} / k_{slow} = (**E**·**R**·**A** + **E** + **R** + **A**) / (**E**·**R** + **R**·**A** + **E**·**A** +1) (Figure 1.11). When both chiral reactants are racemic, the kinetic preference for the "matched" reactions is referred to as mutual kinetic enantioselection (MKE).[71] If one of the reactants is non-racemic, the kinetic preference for the "matched" reaction is referred to as kinetic resolution (KR). Both MKE and KR are the result of unequal rates of reactions of enantiomers with a chiral reactant. The kinetic preference (k_{fast} / k_{slow}) of the "matched" reaction over the "mismatched" reaction depends on the magnitudes of the three stereocontrol elements. As illustrated in the table in Figure 1.11, to have a useful level of selectivity (e.g., ≥10:1), each of the three stereocontrol elements must be strongly biased. For an aldol coupling of racemic reactants (MKE), k_{fast} / k_{slow} can be calculated from the ratio of the sum of all diastereomers resulting from the "matched" reaction to those from the "mismatched" reaction; i.e., = (**24sss** + **24saa** + **24asa** + **24aas**) / (**24ssa** + **24sas** + **24ass** + **24aaa**). It′s worth noting that the multiplicativity rule is necessarily *qualitative* as the stereocontrol elements **E**, **R**, and **A** do not have fixed values and they do not act independently.

Extensive studies on stereoselective aldol couplings of chiral reactants by various research groups suggest that each of the three stereocontrol elements **E**, **R**, and **A** can be modulated (often predictably) by the proper choice of protecting groups, enolate type and ligand, and

additives.[45] Thus, it might be possible to obtain any (or most) of the eight possible diastereomers by appropriate design of the reaction. Toward that end, the aldol coupling illustrated in Figure 1.12 was designed. Some of the important aspects of this design is described below.[69]

1.3.1. A general strategy toward polypropionate synthesis

First, as the structures and stereochemical arrays of the coupling fragments are dictated by the target molecule, change in the structures of the coupling fragments would greatly reduce the efficiency of any synthesis. Instead, if small changes in the structures of coupling fragments (e.g., change in protecting groups, use of cyclic or acyclic substrates) or the reaction conditions can provide improved diastereoselectivity or alter the favored diastereomer, that would be a distinct advantage. Most often, the designed aldol coupling of non-racemic fragments is specific to a single (or small number) of stereoisomers. Thus, synthesis of different stereoisomers often requires different routes and(or) precursors suggesting a more general approach such as the aldol coupling illustrated in Figure 1.12 would be advantageous for polypropionate syntheses. The design in Figure 1.12 would also allow to investigate the aldol couplings of various combinations of ketones (**25-28**) and aldehydes (**29a** and **29b**). For instance, aldol couplings of thiopyran ketones **25** (Y = S; Z = S) with aldehydes **29a** (X = S) or **29b** (X = H,H) would provide aldol adducts which can then be desulfurized to access different diastereomers of polypropionate **34**. On the other hand, similar aldol couplings of the corresponding desulfurized analogues **26** (Y = H,H; Z = H,H) might provide access to other diastereomers of **34**. Therefore, use of various combinations of cyclic (X/Y/Z = S) or acyclic (X/Y/Z = H,H) ketones (**25-28**) or aldehydes (**3**) might provide access to different diastereomers of polypropionate **34** and some of these combinations are presented in this thesis. Second, successful development of methodologies based on this design would allow to perform the aldol couplings of two chiral fragments with kinetic resolution (where only one of the reactants is non-racemic) and avoid the problem of "mismatched" reactions (i.e., low diastereoselectivities, undesired stereoisomers). Aldol couplings with useful levels of kinetic resolution would provide selective access to various diastereomers of **34** in non-racemic form that are useful in polypropionate natural product syntheses. Third, the aldol adducts were purposely designed to incorporate an element of symmetry in the 2D connectivity and occasionally in the 3D structure (e.g., **34**, Pg = H) to facilitate the structure assignments (see sections 2.2.4. and 2.3.5.).

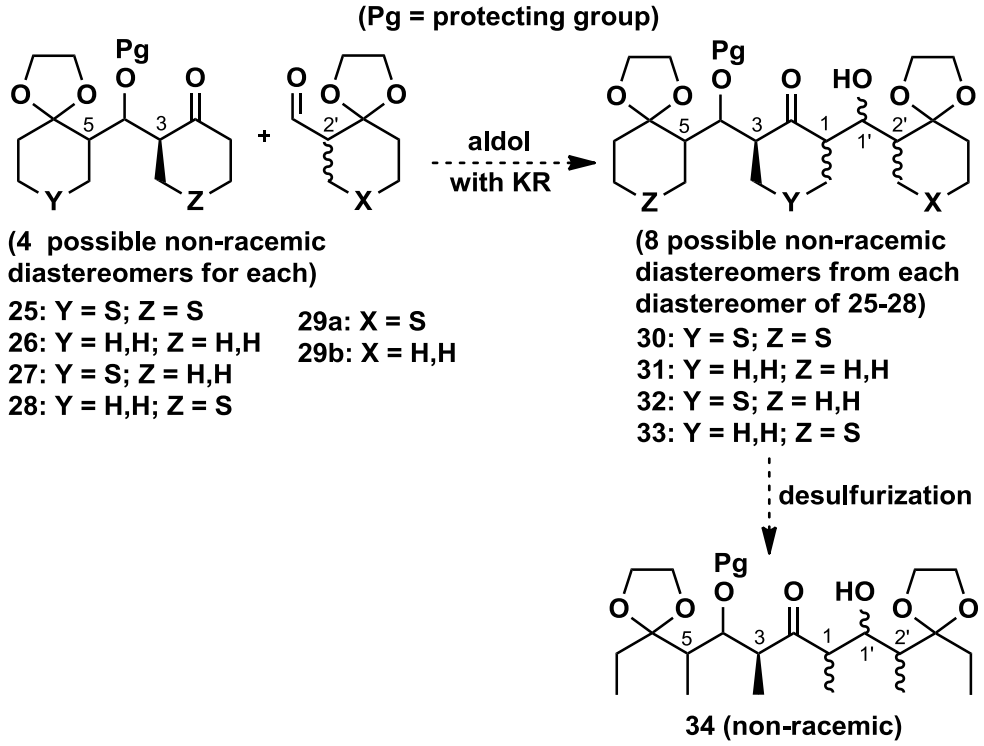


Figure 1.12. Design of aldol couplings with kinetic resolution to access **34**.

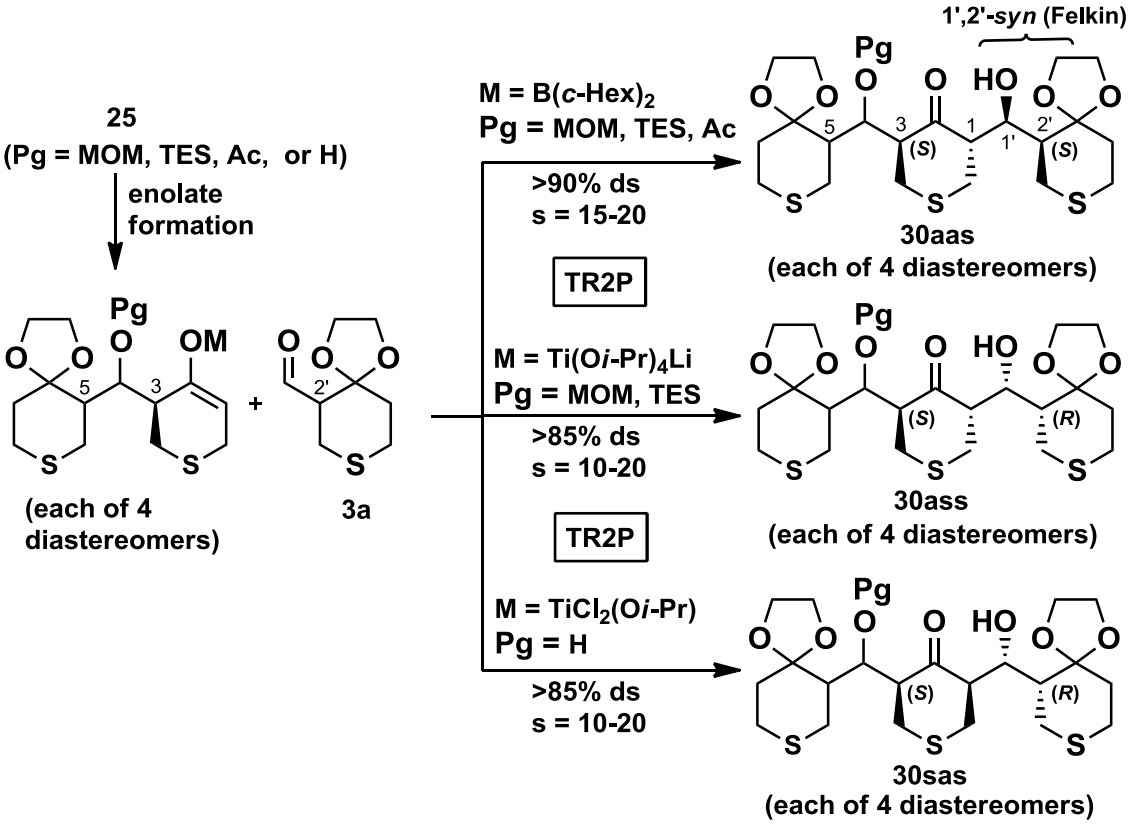
1.3.1.1. Previous work on aldol couplings of 25 and 29a to access 34

Ward *et al*. have extensively investigated the aldol couplings of **29a** with enol borinates and Ti(IV) enolates of **25** (Scheme 1.1).[81-82] In their earlier work,[83] it was demonstrated that the aldol couplings of Ti(IV) enolates of **25** (Pg = H) (generated using $TiCl_3$(O*i*-Pr) and *i*-Pr_2NEt) with **29a** provide selective access to **30sas**. In contrast, the aldol couplings of **25** (Pg = MOM) with **29a** under the same conditions provide two of the eight possible diastereomers: 1,3-*anti*-1,1′-*anti*-1′,2′-*syn* (**30aas**) and 1,3-*anti*-1,1′-*syn*-1′,2′-*syn* (**30ass**). Diastereomers **30aas** (Pg = MOM) result from the *like* combinations of the reactant enantiomers whereas **30ass** (Pg = MOM) result from the *unlike* combinations of the reactant enantiomers. Although both the *like* and *unlike* reactions were highly diastereoselective (only 1 of the 4 possible diastereomers detected in each case), the aldol coupling clearly proceeded with low MKE (k_{like}:k_{unlike} = 0.3-1.5:1). The diastereoface selectivities of both *like* and *unlike* reactions were 1,3-*anti* (with respect to enolate of **25**) and 1′,2′-*syn* (Felkin, with respect to **29a**) selective. However, the relative topicities were unbiased and the observed 1,1′-*anti* adduct **30aas** from the *like* reaction and 1,1′-*syn* adduct **30ass** from the *unlike* reaction simply follow the diastereoface selectivities of the reactants. Therefore, reactions conditions in

which the relative topicity is strongly biased in favor of either the 1,1′-*anti* or the 1,1′-*syn* product were predicted to result in high levels of MKE, thereby providing selective access to **30aas** and(or) **30ass**. It was found that (*c*-Hex)$_2$BCl mediated aldol couplings of **25** (Pg = MOM, TES, Ac) with **29a** provided **30aas** with excellent diastereoselectivities that were interpreted as arising from the highly biased preference of (*E*)-enol borinates of **25** to react with 1,1′-*anti* relative topicity resulting in highly selective MKE in favor of the *like* reaction.[84] Alternatively, reactions of Ti(IV) "ate" enolates of **25** (Pg = MOM, TES) with **29a** gave **30ass** with good to excellent diastereoselectivities due to highly biased 1,1′-*syn* relative topicity under these conditions, leading to MKE in favor of the *unlike* reaction.[84] Similar results were obtained with all four possible diastereomers of **25**. In general, the aldol couplings of the enol borinates were found to proceed with higher MKE than those with the Ti(IV) "ate" enolates. The MKE of the aldol couplings varied widely with the three protecting groups (Pg = MOM, TES and Ac) used and among the four possible diastereomers of **25**. However, for all diastereomers of **25**, at least one example of an enol borinate and of a Ti(IV) "ate" enolate reacting with **29a** with useful levels of MKE (>10:1) in favor of the corresponding *like* and *unlike* reactions, respectively, was achieved.

As predicted, the aldol couplings of enantioenriched **25** with (±)-**29a** proceeded with useful level of KR (generally, s >10). Consequently, each of the four possible diastereomers of **30aas** and **30ass** were obtained in their enantioenriched forms. With three different protecting groups (Pg = MOM, TES and Ac), four diastereomers of ketone (**25**) and two metal enolates (B and Ti); this study together with the work previously accomplished by Ward *et al*.[83] provide a database of results which can be used in the design of stereoselective aldol couplings of related substrates.[81]

Scheme 1.1. Thiopyran route to polypropionates (TR2P): aldol with kinetic resolution (taken from reference 84).



Notwithstanding the extensive studies conducted by Ward *et al*. on the thiopyran route to polypropionates (TR2P)[81] (Scheme 1.1), this study provided selective access to only three (**30aas**, **30ass**, **30sas**) of the eight possible diastereomers of **29** (X = Y = Z = S) (Figure 1.13). The above study clearly demonstrates that the relative topicity (**R**) of an aldol coupling can be modulated by the proper choice of the mediator to access either 1,1′-*syn* or 1,1′-*anti* aldol adducts with 1,3-*anti*-1′,2′-*syn* relative configurations. Extension of this methodology to access the remaining diastereomers of **34** requires identification of suitable substrates and conditions where the two stereocontrol elements **E** and **A** can be modulated predictably to access aldol adducts with 1,3-*syn* or 1,3-*anti* and 1′,2′-*syn* or 1′,2′-*anti* relative configurations. Due to the cyclic nature of the substrates (**25**), the TR2P is restricted to (*E*)-enolates. Switching to the corresponding acyclic analogues **26** would provide access to both (*E*)- and (*Z*)-enolates that in turn might provide access to the remaining aldol diastereomers of **34**. Having selective access to all the possible

diastereomers would not only provide more flexibility in retrosynthetic designs but also allow ready access to sets of diastereomers that could be useful for structure/activity studies or to facilitate determinations of the structures of natural products where the relative and(or) absolute configurations are unknown. Rational design of an aldol coupling of acyclic ketones that proceeds with useful level of KR (ca. s = >10:1) requires identification of suitable substrates and reaction conditions where each of the three stereocontrol elements (**E**, **A**, and **R**) are strongly biased. Toward that end, a comprehensive review of the literature on stereoselective aldol couplings of related acyclic fragments was completed[1] and the findings are summarized below.

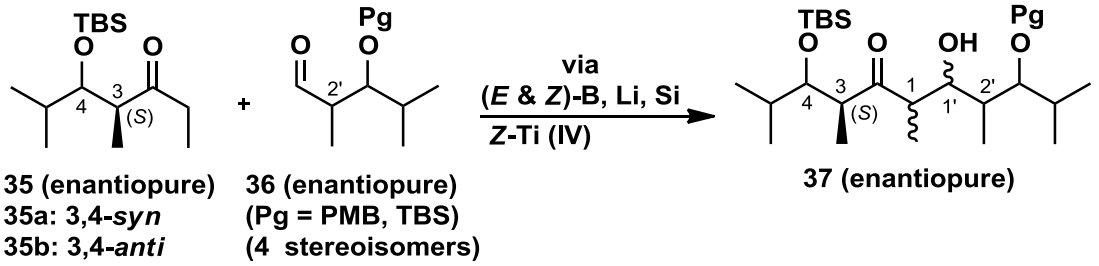


Figure 1.13. Evans' work on stereoselective aldol couplings of acylcic ketones and acyclic aldehydes.

Stereoselective aldol coupling of two non-racemic fragments has been widely used to assemble the carbon skeleton in the late stage of a polypropionate natural product synthesis. Because the coupling of chiral fragments is complicated by double stereodifferentiation(DS),[69] retrosynthetic planning requires judicious selection of a strategic bond for disconnection in which the outcome for the forward reaction can be accurately predicted. Additionally, identification of ketone/aldehyde fragment pairs that are likely to undergo aldol coupling with high diastereoselectivity is crucial for the retrosynthetic design. Evans *et al*. have extensively investigated the stereoselective aldol couplings of (*E*)- and (*Z*)-enol borinates, Li, $SiMe_3$ and Ti(IV) (*Z*)-enolates of enantiopure **35** with the four stereoisomers of enantiopure **36** (Pg = PMB, TBS).[53, 85-86] Others have also investigated stereoselective aldol couplings of related substrates in the context of total syntheses of various natural products.[87-92] These examples together with those reported by Evans *et al*. provide a database that can facilitate the design of stereoselective aldol couplings of related acyclic reactants. Many examples have been reported in the literature where the observed results are in good agreement with those predicted using the above database. Others

have also reported examples where the observed diastereoselectivities were either surprisingly low or different from the predictions. A few representative examples of such instances are summarized in Scheme 1.2. For convenience, the numbering of the natural products is used in Scheme 1.2.

During the total synthesis of erythronolide A, Kochetkov *et al*. designed an aldol coupling of **38** and Li enolate **39** (Scheme 1.2).[93] The reaction was expected to be highly diastereoselective toward **40ass** based on the results reported[92] by Masamune *et al*. for related substrates. Surprisingly, **40ssa** (instead of **40ass**) was formed as the major product in a combined yield of 30% (which also includes a third diastereomer with 10,11-*anti* relative configuration). Variation of protecting groups in aldehyde **38** afforded either no improvement or extremely low diastereoselectivity toward the desired diastereomer.

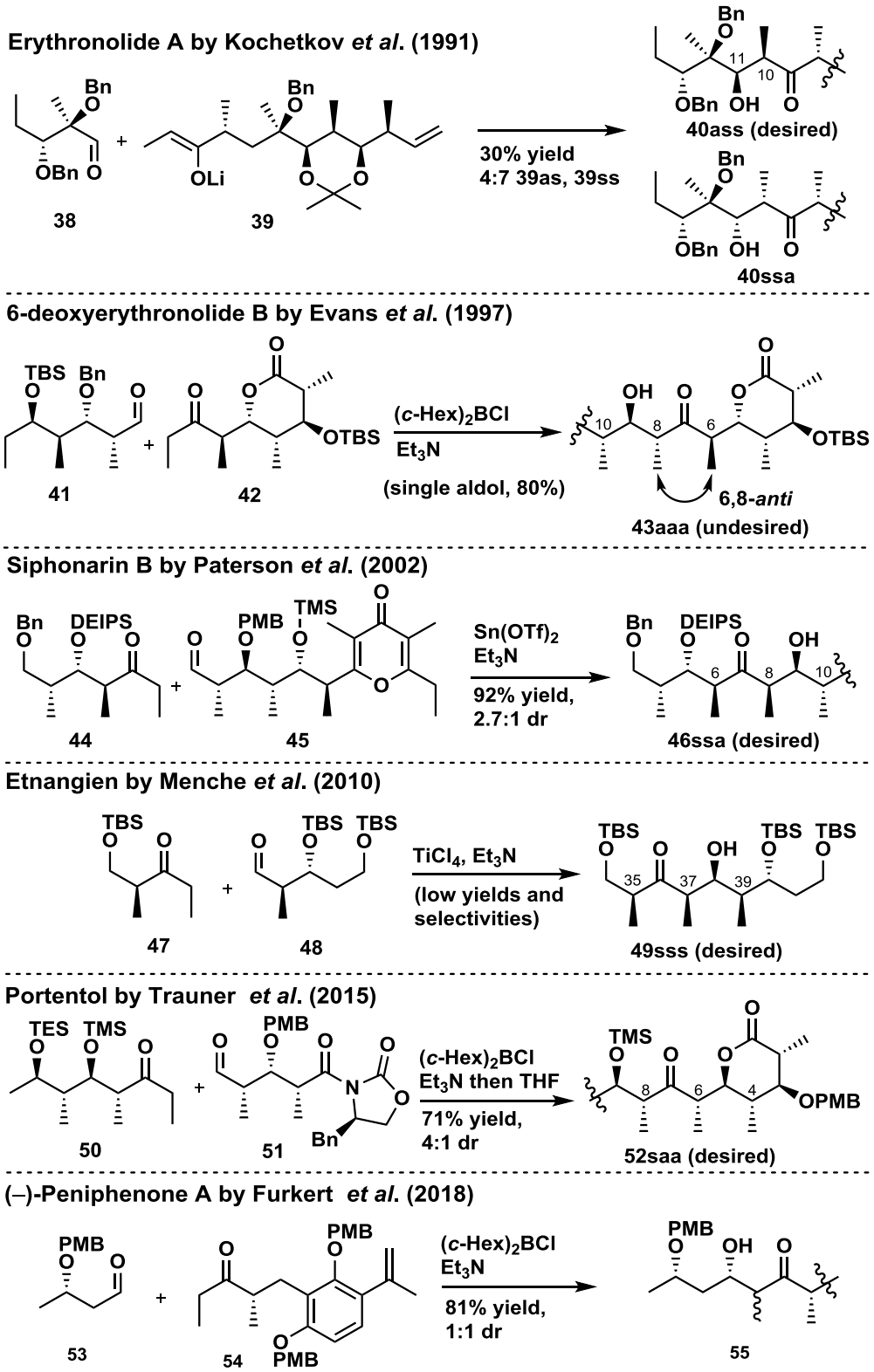
Based on their previous work,[85] Evans and Kim anticipated that the aldol coupling of **41** and **42** (Scheme 1.2) would proceed with high diastereoselectivity in favor of 6,8-*syn*-8,9-*anti*-9,10-*syn* diastereomer (**43sas**, not shown).[64] Unfortunately, the aldol coupling provided a single diastereomer **43aaa** which had 6,8-*anti*-8,9-*anti*-9,10-*anti* relative configurations. Consequently, this approach was abandoned and a new route with a different retrosynthetic disconnection was used to complete the total synthesis of 6-deoxyerythronolide B.[64]

In the total syntheses of siphonarin B and dihydrosiphonarin B, Paterson *et al*.[94] reported a conspicuous example of an aldol coupling of two non-racemic reactants that provided surprisingly low diastereoselectivity. Based on the previous work by Mukaiyama[95] and Paterson,[96] the aldol coupling of **45** with Sn(II)-enolate of **44** was expected to provide high diastereoselectivity toward 6,8-*syn*-8,9-*syn*-9,10-*anti* diastereomer **46ssa** (Scheme 1.2). Surprisingly low diastereoselectivity (2.7:1) was obtained in favor of the desired diastereomer **46ssa** along with two other diastereomers (the minor component of the 2.7:1 mixture represents the sum of the two isomers). To improve the diastereoselectivity, the authors also attempted aldol coupling of differently protected analogues of **44** and **45** via Sn(II)-enolate that also afforded low diastereoselectivity (1.5:1) toward the desired **46ssa**.[94]

During the total synthesis of Etnangien and its methyl ester, Menche *et al*. attempted an aldol coupling of **48** with Ti(IV)-enolate of **47** (Scheme 1.2).[97] Based on their previous work,[98] the coupling was expected to provide high diastereoselectivity toward the desired 35,37-*syn*-37,38-

syn-38,39-*syn* diastereomer **49sss**. In contrast to expectations, the aldol coupling afforded low diastereoselectivities and low yields. Consequently, the route was abandoned.

Scheme 1.2. Aldol couplings of non-racemic fragments with unexpected outcomes in natural product syntheses.



Trauner and Cheng reported the first total synthesis of portentol using the aldol coupling of the (*E*)-enol borinate of **50** with **51** as the key step to assemble the full carbon skeleton (Scheme 1.2).[99] Based on Evans' work,[85] the aldol coupling was expected to afford high diastereoselectivity toward the desired 6,8-*syn*-5,6-*anti*-4,5-*anti* diastereomer. In contrast, low diastereoselectivity (~4:1) was obtained in favor of the desired diastereomer that cyclized during work up to afford lactone **52saa**.

Recently, Furkert *et al*. reported the total synthesis of (−)-peniphenone A using the aldol coupling of **53** and **54** to assemble the full carbon skeleton (Scheme 1.2).[100] Different protecting groups on **53** and **54** and different enolate types were screened under a variety of conditions. For instance, $Sn(OTf)_2/Et_3N$ or chlorodiisopinocampheyl-borane(DIPCl)/Et_3N failed to provide any reaction. Use of LiHMDS gave products in low yield (21%) and with poor diastereoselectivity (1:1.2). Although the use of (c-Hex)$_2$BCl/Et_3N provided improved yields (49-81%), the diastereoselectivities were surprisingly low (1-1.3:1). Under the optimized conditions used in the total synthesis, aldol coupling gave a 81% yield of **55** as a 1:1 diastereomeric mixture.

Careful analysis of the examples illustrated in Scheme 1.2 reveals that the discrepancies between the observed and predicted diastereoselectivities of aldol couplings are often due to structural variations of the coupling fragments (e.g., protecting groups, relative configurations, the presence of additional stereocenters, etc.) compared to the model reactants used for the predictions. The database of available results that have been used to guide retrosynthetic designs has significant gaps in its coverage. For instance, there are few reactions reported for the aldol coupling of **35b** (see Figure 1.13) with isobutyraldehyde compared to similar aldol couplings of **35a**. Surprisingly, aldol couplings of **35b** with **36** have not been reported despite the excellent diastereoselectivity obtained in the aldol coupling of (*Z*)-enol borinate of **35b** with isobutyraldehyde. Aldol couplings Sn(II) (*Z*)-enolates of **35** were not explored nor was the use of alternative protecting groups on **35**. Therefore, the effects of protecting groups, enolate type and geometries, and the presence of additional stereocenters are largely unknown. As a result, the application of the existing database is restricted to a limited number of substrates and its synthetic utility in total syntheses is greatly hampered.

1.4. Objectives

Ward *et al*. have shown that aldol couplings proceeding with kinetic resolution (when one of the reactants is non-racemic) can be rationally designed with the proper knowledge of the stereocontrol elements (Scheme 1.1).[84] Using that approach, three of the eight possible diastereomers of **30** (and of **34**, after desulfurization) were readily available and this strategy was applied to the successful total syntheses of several natural products.[81] The primary objective of the proposed research was to develop methodology to selectively access most (if not all) of the five diastereomers of **34** (Figure 1.12) not accessible from the thiopyran route to polypropionates (TR2P) and thereby increase the stereochemical diversity of aldol couplings depicted in Figure 1.12. Toward that end and as an extension of the TR2P, the acyclic route to polypropionates (AR2P) was designed (Figure 1.14). A specific aim for this research was to design aldol couplings of **29** with enolates of **26** that proceed with useful levels of kinetic resolution. The choice of **26** and **29b** as reactants was based on the obvious relationship with **25** and **29a**; indeed, desulfurization of the known enantiopure diastereomers of **25** is an effective route to enantiopure diastereomers of **26**. As a consequence, the routes to **34** from **25** or **26** differ (at least conceptually) only in the timing of the desulfurization step.

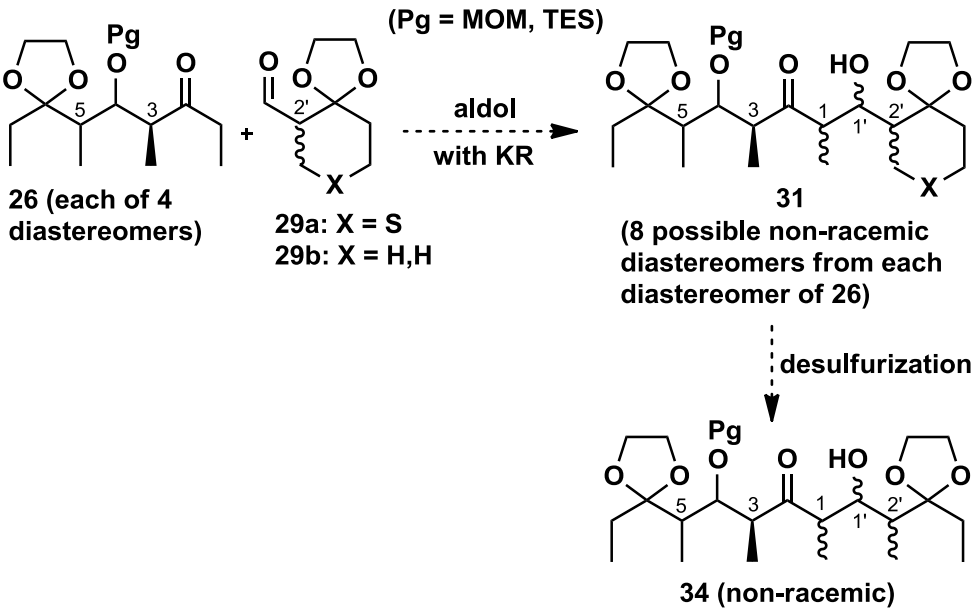


Figure 1.14. Acyclic route to polypropionates (AR2P): aldol with kinetic resolution.

Aldol couplings that proceed with kinetic resolution require three stereocontrol elements highly biased. Successful design of such reactions requires accurate knowledge of how the substrate structure influences the stereocontrol elements. Given the limitations and knowledge gaps in the previous work on the aldol coupling illustrated in Figure 1.14, the initial goal was to establish the structure/diastereoselectivity relationships for aldol additions of the chiral reactants **26** and **29** to model achiral reactants. Accordingly, the factors influencing the diastereoface selectivity of aldol additions to **29a** and **29b** would be revealed by investigating reactions with various enolates of 3-pentanone under various conditions (section 2.2.1.). To determine the structural influences on the diastereoface selectivity and preferred relative topicity of the aldol reactions of **26**, reactions of *i*-PrCHO with various enolates of all four possible diastereomers of **26** (each with two possible protecting groups, MOM and TES) would be investigated (section 2.2.2.). It was expected that the above studies would allow prediction of reaction conditions where aldol couplings of **26** with **29** would proceed with synthetically useful levels of kinetic resolution. The predictions would be initially tested using racemic reactants and those reactions proceeding with high levels of MKE (e.g., >10:1) would be repeated with enantiopure **26** to demonstrate the expected kinetic resolution (KR).

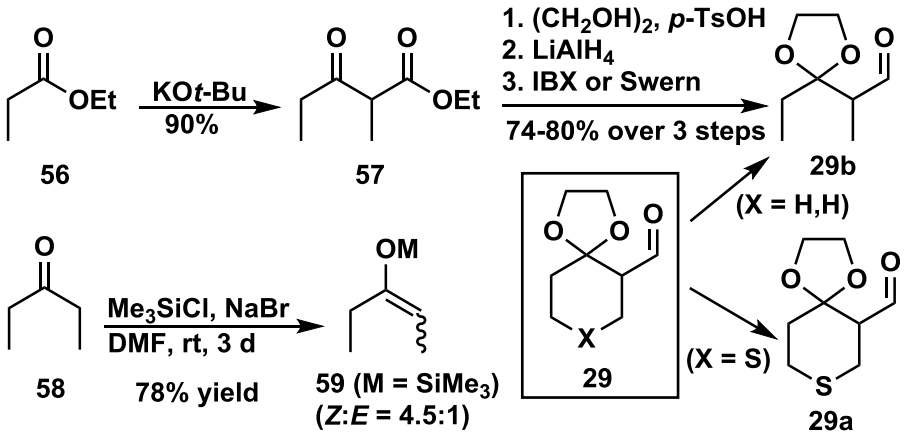
In the course of the above studies, a rare example of a highly stereoselective thermodynamically driven isomerization of Mg(II) aldolates was serendipitously observed (section 2.3.). Consequently, a secondary objective emerged that involved investigating the scope, limitations, and applications of this process.

2. RESULTS AND DISCUSSION

2.1. Preparation of reactants*

The synthesis of required starting materials commenced with the preparation of aldehyde **29b** (Scheme 1.3). According to the method reported by Brown *et al*.,[101] KH was initially used in the preparation of β-keto ester **57** from commercially available ethyl propionate **56** via Claisen self-condensation. Later, KO*t*-Bu was found to be more cost effective to afford **57** in 90% yield with excellent purity. Ketoester **57** was converted to aldehyde **29b** in three steps: protection of the ketone as ethylene acetal; reduction of the ester with $LiAlH_4$; oxidation of the resulting primary alcohol using either IBX (2-iodoxybenzoic acid) or the Swern protocol. The four-step transformation of **56** to **29b** was carried without any column chromatography which makes the synthesis highly scalable. The synthesis of aldehyde **29a** on multigram scale has been reported in the literature.[102]

Scheme 1.3. Synthesis of aldehydes **29** and enol ether **59** (M = $SiMe_3$).



The TMS-enol ether (**59** M = $SiMe_3$) (Scheme 1.3) was prepared by adapting the procedure reported by Iqbal *et al*.[103] Initially, Me_3SiCl (TMSCl) and NaBr were mixed in DMF at room temperature. To the resulting mixture (presumably including TMSBr), 3-pentanone (**58**) and Et_3N were sequentially added at room temperature. After 3 days (90% conversion by ^1H NMR), the mixture was extracted with pentane and the combined organic layers were washed sequentially

* All chiral compounds reported hereafter are racemic unless otherwise noted by the use of a (+) or (−) sign.

with $NaHCO_3$, water and saturated brine solution. Pentane and other organic impurities (i.e., Et_3N and **58**) were removed by fractional distillation and compound **59** (M = $SiMe_3$) was isolated in 78% yield as a 4.5:1 mixture of (*Z*)- and (*E*)-diastereomers.

2.2. Stereoselective synthesis of Felkin aldols

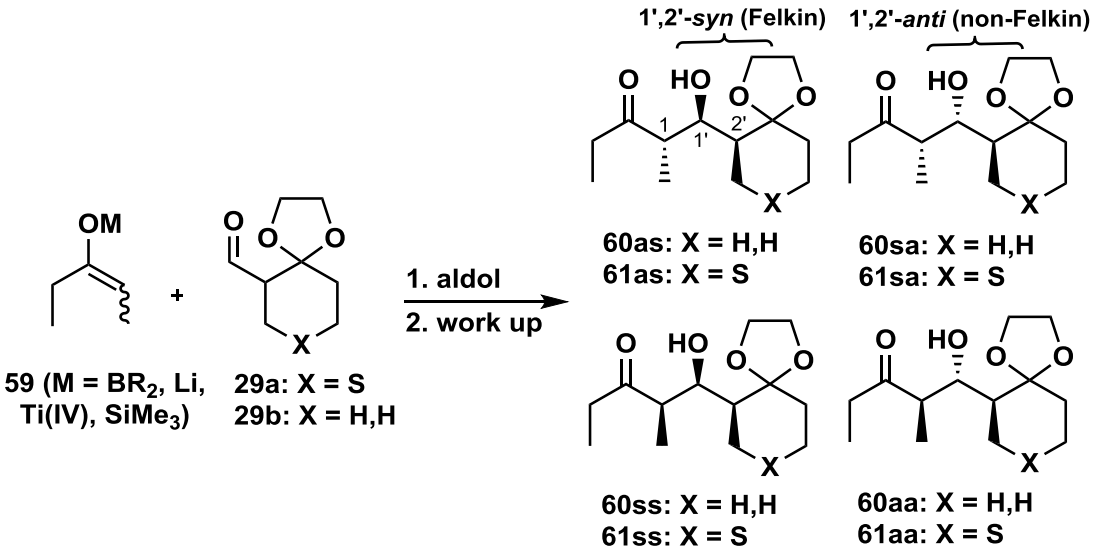
In their previous work (Scheme 1.1),[84] Ward *et al*. have shown that aldol couplings that proceed with kinetic resolution can be rationally designed with substrates and reaction conditions carefully chosen so that all three stereocontrol elements (i.e., diastereoface selectivities of the aldehyde and the ketone derived enolate, and the relative topicity of coupling) are strongly biased. Extension of the scope of this methodology to the acyclic route to polypropionates (see Figure 1.14) requires identification of suitable substrates and reaction conditions such that each of the three stereocontrol elements are sufficiently biased (ca. >10:1) to expect kinetic resolution or where two stereocontrol elements are highly biased and one unbiased, can be exploited to avoid "mismatched" aldol couplings. Toward that end, aldol reactions of chiral aldehydes **29** (Figure 1.12) with achiral enolates and enolates of chiral ketones **26** (Figure 1.12) with achiral aldehydes were performed under a variety of conditions which are described in the following sections. All reactions presented in this part of the thesis were presumed to be under kinetic control because the aldol reactions were performed below room temperature and the observed diastereoselectivity was unchanged with increase in the reaction time.

2.2.1. Diastereoface selectivity of enolate addition to 29

The diastereoface selectivities of enolate addition to chiral aldehydes **29** were evaluated using achiral enolates **59** (M = BR_2, Li, Ti(IV), $SiMe_3$) (Table 2.1). Aldol coupling of **59** and **29b** can form up to four diastereomers **60as**, **60ss**, **60ss**, and **60aa** (Table 2.1). Similarly, aldol coupling of **59** and **29a** can produce to four diastereomers **61as**, **61ss**, **61ss**, and **61aa**. Aldol adducts **60as**, **60ss**, **61as**, and **61ss** have 1′,2′-*syn* relative configuration and are referred to as Felkin aldols. Diastereomers **60sa**, **60aa**, **61sa**, and **60aa** have 1′,2′-*anti* relative configuration and are referred to as non-Felkin aldols. The ratio of Felkin and non-Felkin aldols is a direct measurement of the diastereoface selectivity of enolate addition to the aldehyde (**29**). For coordinating enolates (i.e., M = BR_2, Li, Ti(IV)), the 1,1′-relative configuration of **60** and **61** correlates to the geometry of the enolate according to the closed transition state model (Figure 1.4); that is, (*E*)-enolates form 1,1′-

anti aldols and (*Z*)-enolates form 1,1′-*syn* aldols, predominantly. The results of aldol addition of **59** (M = BR_2, Li, Ti(IV), $SiMe_3$) to **29** are presented in Table 2.1.

Table 2.1. Aldol coupling of achiral enolates **59** with chiral aldehydes **29**.



entry	aldehyde	(*E*/*Z*)-M	aldol adducts (ratio)[a,b]	Felkin:non-Felkin (1′,2′-*syn*:1′,2′-*anti*)	isolated yield[c]
1	**29b**	(*E*)-B(*c*-Hex)$_2$	**6as** (>19:1)	>19:1	92
2	**29a**	(*E*)-B(*c*-Hex)$_2$	**61as** (>19:1)	>19:1	85
3	**29b**	(*Z*)-9-BBN	**60ss**, **60sa** (1.4:1)	1.4:1	14 (69)[d]
4	**29a**	(*Z*)-9-BBN	**61ss**, **61sa** (3.5:1)	3.5:1	48 (33)[d]
5	**29b**	(*Z*)-$TiCl_3$	**60ss**, **60sa** (1:1)	1:1	47 (32)[e]
6	**29a**	(*Z*)-$TiCl_3$	**61ss**, **61sa**, **61as** (9:4.5:1)	2.2:1	81
7	**29b**	(*Z*)-Li	**60ss**, **60as** (1.3:1)	>19:1	90[d]
8	**29a**	(*Z*)-Li	**61ss**, **61as** (2:1)	>19:1	99[d]
9	**29b**	(*Z*)-Ti(O*i*-Pr)$_3$	**60ss**, **60sa**, **60as** (9.5:3.5:1)	3:1	84[d]

10	**29a**	(*Z*)-Ti(O*i*-Pr)$_3$	**61ss**, **61as** (12.3:1)	>19:1	81[d]
11	**29b**	(*Z*)-SiMe$_3$ (BF_3·OEt_2)	**60ss**, **60as** (10:1)	>19:1	63
12	**29a**	(*Z*)-SiMe$_3$ (BF_3·OEt_2)	**61ss**, **61as** (3:1)	>19:1	99[d]
13	**29b**	(*Z*)-SiMe$_3$ ($MgBr_2$·OEt_2)	**60aa**, **60sa** (1:1)	<1:19	42(39)[e]
14	**29a**	(*Z*)-SiMe$_3$ ($MgBr_2$·OEt_2)	**61aa, 61sa** (6.3:1)	<1:19	76(17)[d]

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting aldehyde in the crude reaction mixture by ^{1}H NMR. [c]Isolated yield of the major aldol adduct. [d]Isolated yield of the mixture of aldol adducts. [e]Isolated yield of **60sa**.

Enolization of **58** using (*c*-Hex)$_2$BCl and Et_3N has been investigated by Brown *et al*.[104] Following the reported[104] procedure, the (*E*)-enol dicyclohexylborinate **59** (M = B(*c*-Hex)$_2$) was generated from **58** by treatment with (*c*-Hex)$_2$BCl and Et_3N at 0 °C for 1 h. To the resulting mixture was added **29** at −78 °C (entries 1 and 2, Table 2.1).* After 16-17 h, standard oxidative work up gave crude products whose ^{1}H NMR spectra showed the presence of a single (>19:1 dr) aldol adduct **60as** from **29b** and **61as** from **29a**. Formation of a single diastereomer indicates high diastereoface selectivities for the enolate additions to **29**.†

Selective formation of the (*Z*)-enol borinate **59** (M = 9-BBN) from **58** using 9-BBNOTf and Et_3N with >99:1 *Z*:*E* selectivity was reported by Brown *et al*.[105] Following the reported[105] procedure, enolization of **58** was performed using 9-BBNOTf and Et_3N at room temperature followed by addition of **29** at −78 °C (entries 3 and 4, Table 2.1). Only 1,1′-*syn* aldols were detected by ^{1}H NMR of the crude reaction mixtures consistent with the selective formation of (*Z*)-enolate

* Reaction of **29b** was performed by Kundu, D.

† In this thesis, <5:1 selectivity will be referred to as low, 5-10:1 selectivity as moderate, and >10:1 selectivity as high.

as previously reported.[105] Interestingly, both 1′,2′-*syn* (Felkin) and 1′,2′-*anti* (non-Felkin) aldols were detected suggesting that diastereoface selectivities of aldol additions to **29** were lower with (*Z*)-enol borinate compared to that with (*E*)-enol borinate.[48] Moreover, the amount of 1′,2′-*anti* (non-Felkin) aldols from **29b** was greater than that from **29a**. This observation might be useful in accessing non-Felkin aldols of enantiopure **29b** in reaction with enantiopure (*Z*)-enol borinates in "mismatched" aldol couplings.

Evans *et al*. have investigated the soft enolization of **58** using $TiCl_4$ and tertiary amine bases such as *i*-Pr_2NEt or Et_3N.[106] The reported *Z*:*E* selectivity was higher (92:8) using *i*-Pr_2NEt than Et_3N (87:13).[106] Therefore, *i*-Pr_2NEt was selected for the current investigation. Adapting the reported[106] procedure, the Ti(IV) enolate **59** (M = $TiCl_3$) was generated from **58** and the resulting mixtures were treated with **29** at −78 °C. After 1 h, the reactions were quenched by addition of saturated NH_4Cl and the mixtures were extracted with CH_2Cl_2. The crude products were analyzed by ^1H NMR and the results are presented in entries 5 and 6 (Table 2.1). Both 1′,2′-*syn* (Felkin) and 1′,2′-*anti* (non-Felkin) aldols were detected from both aldehydes **29a** and **29b** suggesting low diastereoface selectivities for the aldol additions under these conditions. The observed ratios (≥93:7) of the 1,1′-*syn* and 1,1′-*anti* aldols were consistent with the reported[106] *Z*:*E* ratio (92:8) of the Ti(IV) enolate **59** (M = $TiCl_3$). Similar to the (*Z*)-enol borinate **59** (M = 9-BBN), the aldol addition of the Ti(IV) (*Z*)-enolate **59** (M = $TiCl_3$) to **29b** gave increased amounts of 1′,2′-*anti* (non-Felkin) product compared to that obtained from similar addition to **29a**.

Formation of the Li (*Z*)-enolate **59** (M = Li) from **58** using $(Me_3Si)_2NLi$ in THF has been reported by Heathcock[107] and Masamune.[92] The reported *Z*:*E* diastereoselectivities range from 66:34 to 70:30 with the Li (*Z*)-enolate being the major product, as determined by quenching the Li enolates with Me_3SiCl/Et_3N. Using similar conditions, enolization of **58** was carried out at −78 °C followed by additions of **29**. After 2 min, the reactions were quenched with saturated NH_4Cl and extracted with CH_2Cl_2. The crude products were analyzed by ^1H NMR and the results are presented in entries 7 and 8 (Table 2.1). Only 1′,2′-*syn* (Felkin) aldols were detected from both **29a** and **29b**. Both 1,1′-*syn* (**60ss** and **61ss**) and 1,1′-*anti* (**60as** and **61as**) aldols were present in ratios of 1.3-2:1 which is loosely comparable to the reported ratio of Li (*Z*)- and (*E*)-enolates.[92, 107]

The aldol couplings of Ti(IV) (*Z*)-enolate **59** (M = Ti(O*i*-Pr)$_3$) with **29** were also investigated. Enolate **59** (M = Ti(O*i*-Pr)$_3$) was obtained by transmetallation of the corresponding

Li enolate with freshly prepared $TiCl(O\textit{i}\text{-}Pr)_3$ at −42 °C for 2 h. The resulting mixtures were treated with **29** at −78 °C for 3 h. The results are summarized in entries 9 and 10 (Table 2.1). The ^{1}H NMR of the crude reaction mixtures showed the presence of 1,1′-*syn* and 1,1′-*anti* aldols in a 12-13:1 ratios for both aldehydes **29a** and **29b** suggesting predominant formation of Ti(IV) (*Z*)-enolate under these conditions. Like chlorotitanium (*Z*)-enolate **59** (M = $TiCl_3$), the aldol addition of **59** (M = $Ti(O\textit{i}\text{-}Pr)_3$) to **29b** provided both 1′,2′-*syn* (Felkin) and 1′,2′-*anti* (non-Felkin) aldols. In contrast, similar addition to **29a** was highly 1′,2′-*syn* (Felkin) selective. Therefore, it can be concluded that the diastereoface selectivity of enolate addition to **29a** was higher compared to similar addition to **29b**. Entry 9 in Table 2.1 suggests that $TiCl_n(O\textit{i}\text{-}Pr)_{4-n}$ (n = 1-3) mediated aldol coupling might provide access to 1′,2′-*anti* (non-Felkin) aldols and this will be discussed in section 2.3.2.

Mukaiyama aldol couplings of **29** and **59** (M = $SiMe_3$) were initially investigated with $BF_3{\cdot}OEt_2$ as the promoter. The reactions were performed with a 4.5:1 mixture of (*Z*)-and (*E*)-enol ethers at −78 °C in CH_2Cl_2 and the results are presented in entries 11 and 12 (Table 2.1). Consistent with the Felkin-Anh transition state model (Figure 1.8), only 1′,2′-*syn* (Felkin) aldols were detected by ^{1}H NMR of the crude products from both **29a** and **29b**.

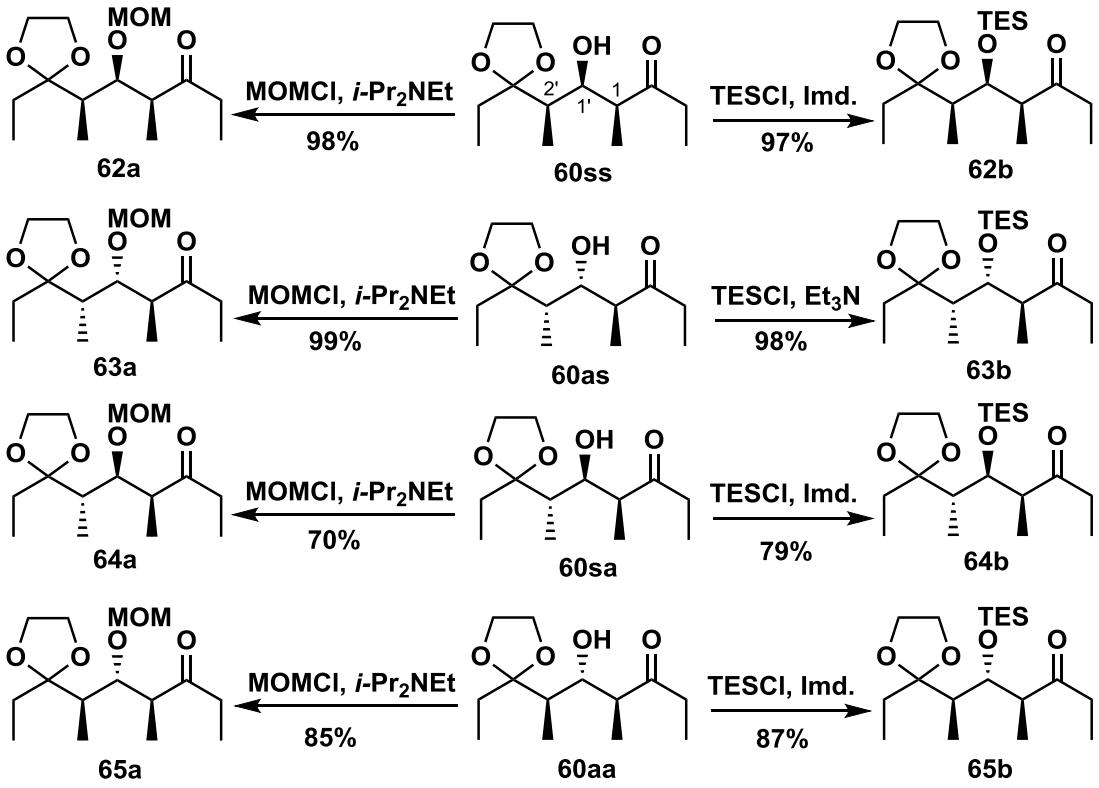
Ward *et al*. have demonstrated exclusive chelation control using $MgBr_2{\cdot}OEt_2$ in Mukaiyama aldol coupling of **29a** with trimethylsilyl enol ether of achiral thiopyranone.[108] Using similar conditions, chelation controlled Mukaiyama aldol couplings of **29** and **59** (M = $SiMe_3$, 4.5:1 *Z*, *E*) were performed in the presence of $MgBr_2{\cdot}OEt_2$ and the results are presented in entries 13 and 14 (Table 2.1).* Only 1′,2′-*anti* (non-Felkin) aldols were detected by ^{1}H NMR of the crude products. Both 1,1′-*syn* (**60sa**) and 1,1′-*anti* (**60aa**) diastereomers were obtained from **29b** in 1:1 ratio. The addition of **59** (M = $SiMe_3$) to **29a** was more diastereoselective (6:1 dr) favoring **61aa** compared to similar addition to **29b**. The scope of this reaction was further explored with various chiral enol ethers and the results will be discussed in section 2.3.3. For both $BF_3{\cdot}OEt_2$ and $MgBr_2{\cdot}OEt_2$ promoted Mukaiyama aldol couplings, the ratios of 1,1′-*syn* and 1,1′-*anti* aldols

* Reaction of **3a** was performed by Biniaz, M.

illustrated in Table 2.1 (entries 11-14) do not correlate to the starting ratio of (*Z*)- and (*E*)-enol ethers which is consistent with the open transition state model (Figure 1.5).

2.2.1.1. Structure determination of 60 and 61

Scheme 2.1. Preparation of MOM and TES protected derivatives of **60**.*

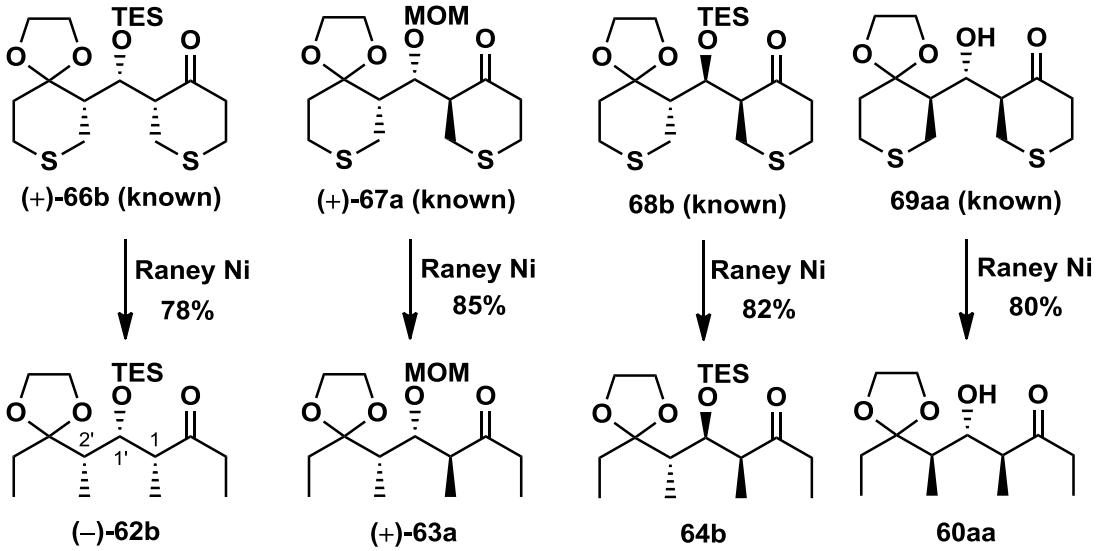


To establish the structures of all four possible diastereomers of aldol adducts obtained from **29b**, each aldol adduct was converted to the corresponding MOM (methoxy methyl, CH_3OCH_2) and TES (triethylsilyl, Et_3Si) protected derivatives (Scheme 2.1). The relative configurations of all four acyclic aldols **60** were established by ^1H and ^{13}C NMR correlations to the known compounds. Ketone **(−)-62b** has previously been synthesized from known ketone **(+)-66b**[109] (Pg = TES) via desulfurization. The ^1H and ^{13}C NMR data of **62b** were identical with those from **(−)-62b**[109] suggesting the same 1,1′-*syn*-1′,2′-*syn* (ss) relative configurations for **62b**, **62a** and

* Derivatizations of **60as**, **60sa**, and **60aa** were performed by Kundu, D. and Biniaz, M.

the precursor **60ss**. Ketone **(+)-63a**[110] has previously been synthesized from known ketone **(+)-67a**[110] (Pg = MOM) via desulfurization.[110] The ^{1}H and ^{13}C NMR data of **63a** were identical with those from **(+)-63a** confirming the 1,1′-*anti*-1′,2′-*syn* (as) relative configurations for **63a**, **63b** and **60as**. Based on the same analogy, the structures of **64a**, **64b** and **60sa** were established as 1,1′-*syn*-1′,2′-*anti* (sa) by correlating **64b** with the known ketone **68b**[84] (Pg = TES). Similarly, desulfurization of known ketone **69aa**[108] (Pg = H) provided **60aa** and confirmed its relative configurations as 1,1′-*anti*-1′,2′-*anti* (aa) and thereby confirming the same relative configurations for **65a** and **65b**.

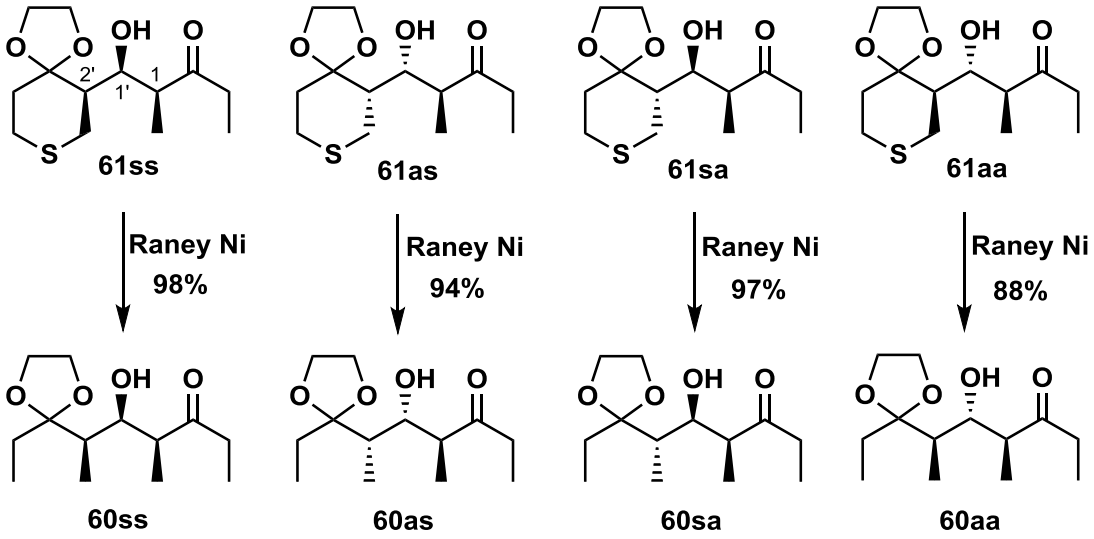
Scheme 2.2. Structure determination by desulfurizations of **67-69**.*



The structures of all the cyclic aldols **61** derived from **29a** were confirmed by correlation to the acyclic aldols **60** for which the structures were already established in Scheme 2.2. As illustrated in Scheme 2.3, desulfurization of each of the four aldol diastereomers of **61** provided the corresponding aldol diastereomers of **60**, establishing their respective 1,1′-1′,2′-relative configurations.

* Desulfurizations of **(+)-67a**, **68b** and **69aa** were performed by Kundu, D. and Biniaz, M.

Scheme 2.3. Structure determination of cyclic aldols **61**.



2.2.2. Diastereoface selectivity of aldehyde addition to enolates of 62-65

Having evaluated the diastereoface selectivities for the enolate additions to aldehydes **29**, the next goal was to study the diastereoface selectivities of aldehyde additions to enolates of chiral ketones **62-65**. The diastereoface selectivities were evaluated by the addition of isobutyraldehyde (*i*-PrCHO) (**70**) to various metal enolates (BR_2, Li, Ti(IV)) of ketones **62-65** (Figure 2.1). Aldol couplings of **70** with each ketone can form up to four diastereomers **sa**, **aa**, **as**, and **ss**. As a result, there are total 32 possible aldol adducts from the eight possible ketones **62-65** (Pg = MOM, TES). The ratio of 1,3-*syn* to 1,3-*anti* aldols is a direct measurement of the diastereoface selectivities of the aldehyde additions to enolates of **62-65**. Extensive optimization was carried out to find suitable conditions to selectively access (*E*)- and (*Z*)-enolates of ketones **62-65**. The optimized conditions for each substrate are presented below and the results are summarized according to the enolate type used.

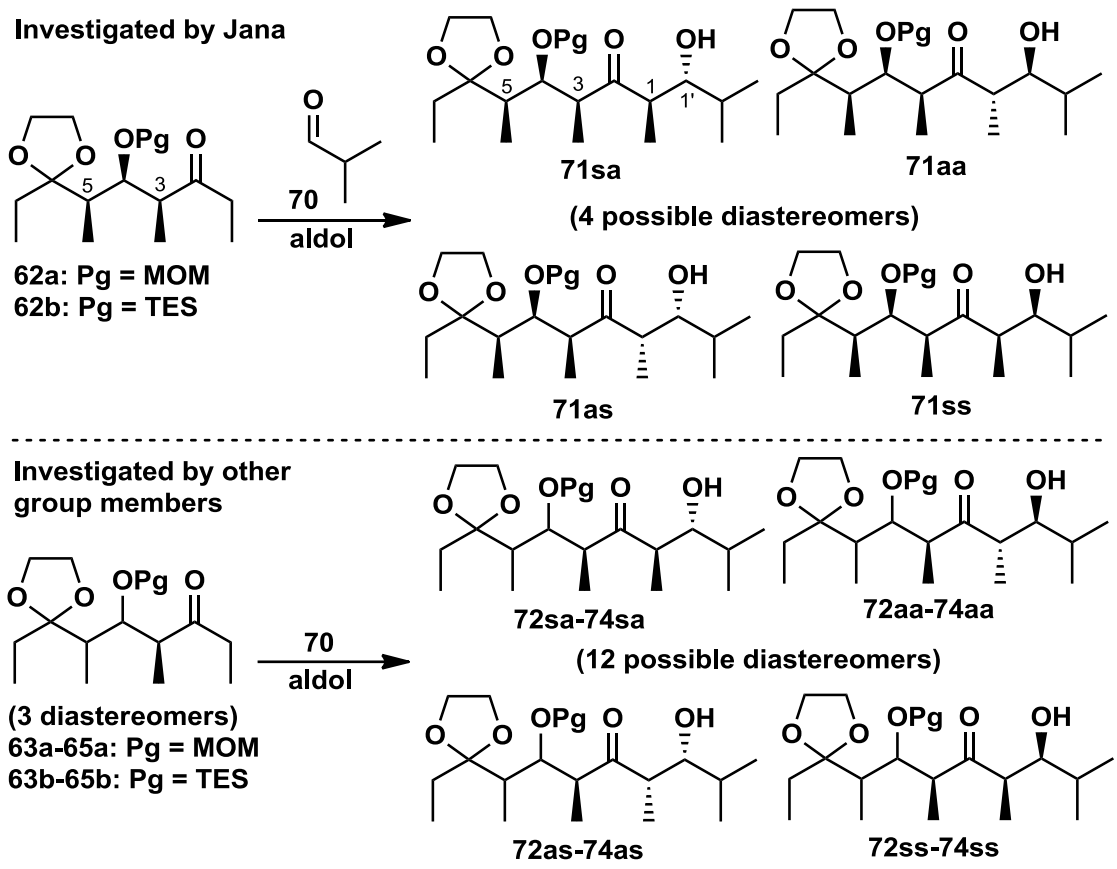
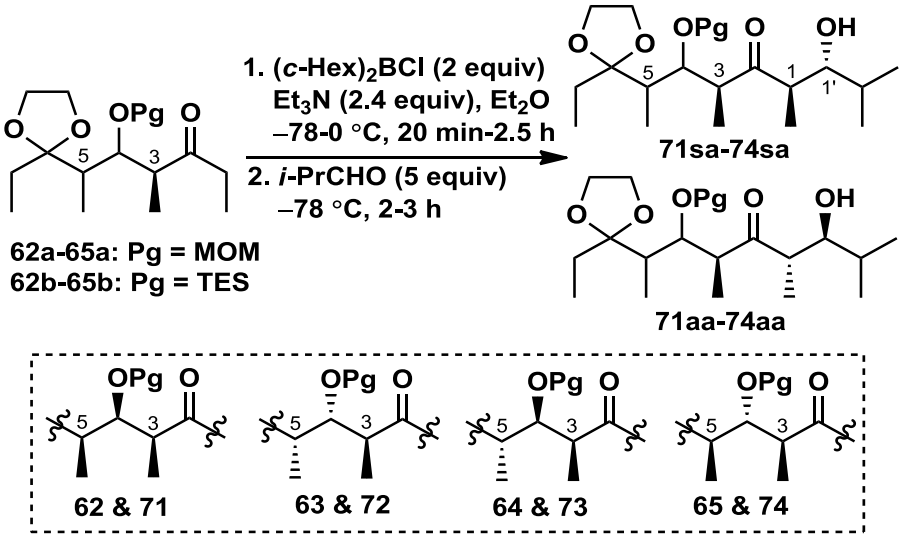


Figure 2.1. Aldol couplings of chiral ketones **62-65** with **70**.

The use of (*c*-Hex)$_2$BCl and Et$_3$N to access (*E*)-enol borinates of ethyl ketones are well known in the literature and provide (*E*)-enolates predominately.[5] Suitable conditions were found that gave selective access to (*E*)-enol borinates of **62-65** with high diastereoselectivities (>19:1 *E*, *Z*). The aldol additions of **70** with (*E*)-enol borinates of **62-65** are illustrated in Table 2.2. Using the procedure reported by Ward *et al*.,[14] initial attempts at enolization of **62a** at lower temperatures (e.g., −50 ˚C, −78 ˚C) were unsuccessful. Performing the enolization at 0 °C for 2 h followed by addition of **70** at −78 ˚C provided aldol **71sa** (Pg = MOM) with high conversion (>90%) and excellent diastereoselectivity (>20:1) (entry 1). Unfortunately, the mixture of aldol **71sa** (Pg = MOM) and the starting ketone **62a** was inseparable. Subjecting the crude reaction mixture to TESCl and imidazole in DMF provided the corresponding TES-protected derivative of aldol **71sa** (Pg = MOM) which was easily separable from **62a**. After purification, the TES-protected derivative of aldol **71sa** (Pg = MOM) was treated with pyridine hydrofluoride (HF·Py) to afford **71sa** (Pg = MOM) in 64% yield (from **62a**).

Table 2.2. Aldol couplings of (*E*)-enol borinates of **62-65** with **70**.*



entry	ketone	enolization conditions	(sa:aa)[a]; convn[a,b]	(1,3-*syn*:1,3-*anti*)[c]	isolated yield[d]
1	**62a**	0 ˚C, 2 h	>19:1; 95%	>19:1	64[e]
2	**62b**	0 ˚C, 0.5 h	3.5:1; 95%	3.5:1	60[e,f]
3	**63a**	−42 °C, 2 h	2:1; 95%	2:1	62 (26)
4	**63b**	−42 °C, 1.5 h	>19:1; 85%	>19:1	80
5	**64a**	−78 °C, 1 h	>19:1; 95%	>19:1	87
6	**64b**	−42 °C, 2.5 h	17:1; 85%	17:1	83
7	**65a**	−78 °C, 2.5 h	6:1; 90%	6:1	70 (6)
8	**65b**	0 ˚C, 20 min	>19:1; 70%	>19:1	62

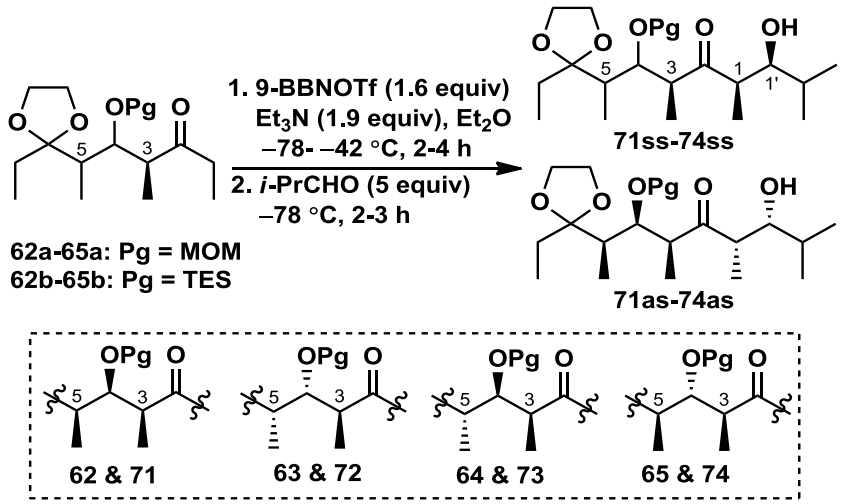
[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Calculated from the ratio of 1,3-*syn* to 1,3-*anti* aldol adducts of (*E*)-enol borinates. [d]Isolated yield of the major aldol adduct (isolated yield of minor adduct in parentheses). [e]Lower yield due to difficult fractionation. [f]Plus 31% of a 2:1 mixture of **71sa** (Pg = TES) and **71aa** (Pg = TES), respectively.

* Results presented in entries 3-8 (Table 2) were obtained by Kundu, D. and Biniaz, M.

Enolization of **62b** was performed under conditions similar to those used for **62a** (Table 2.2). After enolization of **62b** at 0 °C for 30 min, **70** was added to the reaction mixture at −78 ˚C. After 2 h, standard oxidative work up afforded crude product whose ^{1}H NMR showed the presence of a 3:1 mixture of **71sa** (Pg = TES) and **71aa** (Pg = TES). The results in entries 1 and 2 show the potentially significant effect of the protecting group. Aldol couplings of (*E*)-enol borinates of **63-65** with **70** were investigated by other group members under a variety of conditions and the results are presented in entries 3-8. In all the examples shown in Table 2.2, the 1,3-*syn*-1,1′-*anti* (**sa**) aldol was formed as the major product. The diastereoselectivities of aldol additions varied widely, ranging from 2:1 to >19:1. Excellent diastereoselectivities (>19:1) were obtained for at least one of the two possible substrates (Pg = MOM or TES) of the four possible diastereomers of ketones **62-65**.

Aldol additions of (*Z*)-enol borinates of chiral ketones with chiral aldehydes is not a well investigated area in organic syntheses. Scattered examples of aldol couplings of (*Z*)-enol borinates of chiral ketones with achiral aldehydes are reported in the literature.[111-113] The lack of literature precedents is most likely due to the high reactivity of 9-BBNOTf which makes it incompatible with many functional groups, extensive optimization is required for efficient enolization and the *Z*:*E* ratios are often quite low.[48] Table 2.3 represents the optimized conditions for the selective (>19:1 *Z*, *E*) formation of (*Z*)-enol borinates of **62-65** obtained by treatment with 9-BBNOTf and Et_3N. Aldehyde **70** was added to the resultant enolates and after 2-3 h, standard oxidative work up provided the crude products that were analyzed by ^{1}H NMR and the results are summarized in Table 2.3.

Table 2.3. Aldol couplings of (*Z*)-enol borinates of **62-65** with **70**.*



entry	ketone	enolization	(ss:as)[a]; convn[a,b]	(1,3-*syn*:1,3-*anti*)[c]	isolated yield[d]
1	**62a**	−78 ˚C, 2 h	>19:1; 90%	>19:1	77
2	**62b**	−78 ˚C, 4 h	>19:1; 80%	>19:1	67
3	**63a**	−78 ˚C, 2 h	4:1; 70%	4:1	53 (13)
4	**63b**	−42 ˚C, 2 h	9:1; 75%	9:1	62 (7)
5	**64a**	−78 ˚C, 2.5 h	>19:1; 95%	>19:1	86
6	**64b**	−42 ˚C, 4 h	1.7:1; 75%	1.7:1	41 (22)
7	**65a**	−78 ˚C, 2.5 h	>19:1; 95%	>19:1	77
8	**65b**	−42 ˚C, 4 h	2:1; 70%	2:1	38 (17)

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Calculated from the ratio of 1,3-*syn* to 1,3-*anti* aldol adducts of (*Z*)-enol borinates. [d]Isolated yield of the major aldol adduct (isolated yield of minor adduct in parentheses).

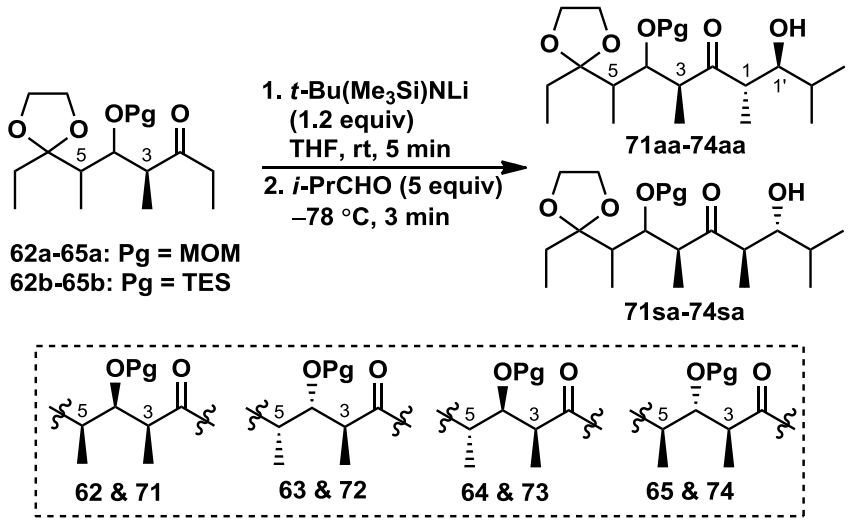
* Results presented in entries 3-8 (Table 3) were obtained by Kundu, D. and Biniaz, M.

The aldol couplings of **62** with **70** under these conditions provided a single aldol adduct (>19:1 dr) (entries 1 and 2, Table 2.3). The aldol additions of (*Z*)-enol borinates of **63-65** with **70** were also investigated and the results are summarized in entries 3-8.* Similar to **62**, aldol additions of **64a** and **65a** provided excellent diastereoselectivities (>19:1). In contrast, low diastereoface selectivity (4:1) was obtained with **63a**. Except for **62b**, the aldol additions of (*Z*)-enol borinates of **63b-65b** provided low (≤2:1) to moderate (9:1) diastereoselectivities. In all cases, the 1,3-*syn*-1,1′-*syn* (**ss**) aldol adduct was the major product and the 1,3-*anti*-1,1′-*syn* (**as**) adduct was the minor. The ratio of **ss** and **as** aldol adducts varied widely ranging from 2:1 to >19:1. Five of the eight possible ketones were highly selective (≥9:1) toward **ss** aldol adduct (entries 2-5 and entry 7).

Few examples of aldol reactions of Li (*E*)-enolates of chiral ketones are reported in the literature.[86] A single example of an aldol coupling of Li (*E*)-enolate of a chiral ethyl ketone with isobutyraldehyde (**70**) has been reported in the literature by Evans *et al*.[86] The aldol coupling provided a mixture of all four possible diastereomers with the 1,3-*syn*-1,1′-*anti* (**sa**) aldol adduct being the major product.[86] According to the report of Xie *et al*.,[114] the reactions of achiral ethyl ketones with LiN(Me$_3$Si)*t*-Bu provide Li (*E*)-enolates with high diastereoselectivities. Due to the lack of literature precedents, aldol reactions of the Li (*E*)-enolates of all eight ketones (**62-65**), each prepared by reaction with LiN(Me$_3$Si)*t*-Bu, with isobutyraldehyde (**70**) were investigated (Table 2.4). The ratios of (*E*)- and (*Z*)-enolates were confirmed by reaction with TMSCl/Et$_3$N at −78 °C and work up after 3 minutes provided the crude trimethylsilyl enol ethers. The ^{1}H NMR analyses showed low (≤3.5:1) to moderate (7-9:1) ratios of Li (*E*)- and (*Z*)-enolates. Addition of **70** to the above enolate mixtures at −78 °C followed by work up after 3 min gave the crude products that were analyzed by ^{1}H NMR. The results are summarized in Table 2.4.

* Results presented in entries 3-8 (Table 2) were obtained by Kundu, D. and Biniaz, M.

Table 2.4. Aldol couplings of Li (*E*)-enolates of **62-65** with **70**.*



entry	ketone	enolate[a] (*E*:*Z*)	(aa:sa:as:ss)[b]; convn[b,c]	(1,3-*syn*:1,3-*anti*)[d]	isolated yield[e]
1	**62a**	3.4:1	12:5:3:2; 90%	2.4:1	21 (24)
2	**62b**	2.8:1	5:4:2:1; 90%	1.3:1	14 (17)
3	**63a**	9:1	16:ND[f]:1:1; 95%	>19:1	79
4	**63b**	9:1	ND[f]:9.5:ND[f]:1; 95%	<1:19	85
5	**64a**	7:1	8:4:1:1; 90%	2:1	41 (25)
6	**64b**	2:1	ND[f]:5:1:1.3; 95%	<1:19	59
7	**65a**	3.5:1	ND[f]:3.5:1:ND[f]; 95%	<1:19	70
8	**65b**	3.3:1	1:20:3.3:3; 90%	1:20	63

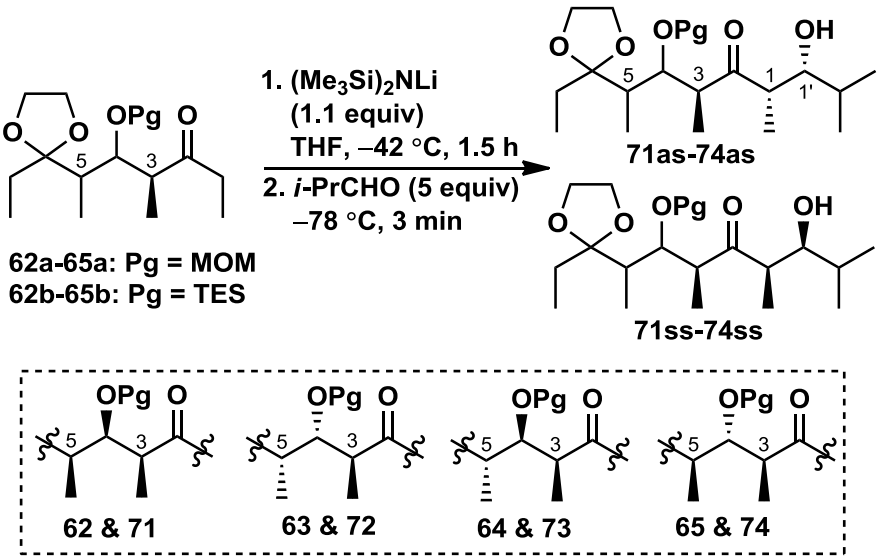
[a]Determined by ^{1}H NMR of the crude enol ethers obtained by addition of TMSCl/Et_3N (3:1) to the enolate at −78 °C. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [d]Calculated from the ratio of 1,3-*syn* to 1,3-*anti* aldol adducts of Li (*E*)-enolates (i.e., the ratio of **aa** and **sa** aldol adducts). [e]Isolated yield of the major 1,1′-*anti* aldol adduct (isolated yield of the minor 1,1′-*anti* aldol adduct in parentheses). [f]Not detected.

* Results in presented entries 3-8 (Table 2.4) were obtained by Kundu, D. and Biniaz, M.

Except for **65a**, the aldol couplings of all MOM protected ketones provided the 1,3-*anti*-1,1′-*anti* (**aa)** aldol adduct as the major product (entries 1, 3, and 5, Table 2.4). Whereas, the 1,3-*syn*-1,1′-*anti* (**sa)** aldol adduct was the major product for all the TES protected ketones (entries 2, 6, and 8), except for **62b**. In all cases, the presence of 1,1′-*syn* aldols (**ss** and(or) **as**) presumably resulting from Li (*Z*)-enolates were detected. The ratios of 1,1′-*anti* and 1,1′-*syn* aldols were in good agreement with the *E*:*Z* ratios of the Li enolates. The reported ratios of 1,3-*syn* and 1,3-*anti* products refer exclusively to those from the Li (*E*)-enolates (i.e., the ratio of **aa** and **sa** products).

Li (*Z*)-enolates of **62-65** were generated by treating the ketones with freshly prepared $(Me_3Si)_2NLi$ at −42 °C. The *Z*:*E* ratios of the corresponding Li enolates were determined by quenching the reaction mixtures with TMS/Et_3N at −78 °C (Table 2.5). High (>10:1) diastereoselectivities were obtained in favor of Li (*Z*)-enolates for all the ketones, except for **63b**. The reactions of Li (*Z*)-enolates of **62-65** with **70** were performed at −78 °C for 3 min and the results are summarized in Table 2.5. Excellent conversions (≥90%) were obtained in all cases and the ratios of 1,1′-*syn* and 1,1′-*anti* aldols closely matched the corresponding *Z*:*E* ratios of the Li enolates. As shown in entries 1, 2, 4, and 6, the presence of 1,1′-*anti* aldols (**aa** or **sa**) presumably resulting from Li (*E*)-enolates were detected. In those cases, the reported ratios of 1,3-*syn* and 1,3-*anti* products refer exclusively to those from the Li (*Z*)-enolates (i.e., the ratio of **ss** and **as** products). The diastereoselectivities of aldol reactions were low (1.5:1) to moderate (8:1). Except for **63a**, aldol couplings of all other ketones resulted 1,3-*anti*-1,1′-*syn* (**as**) aldol as the major product and 1,3-*syn*-1,1′-*syn* (**ss**) aldol as the minor. The results shown in Table 2.5 are consistent with the results reported by McCarthy *et al*.[115] During their investigation of the aldol couplings of Li (*Z*)-enolates of related ketones with **70**, the 1,3-*anti*-1,1′-*syn* (**as**) aldol adducts were found to be the major diastereomer.

Table 2.5. Aldol couplings of Li (*Z*)-enolates of **62-65** with **70**.*



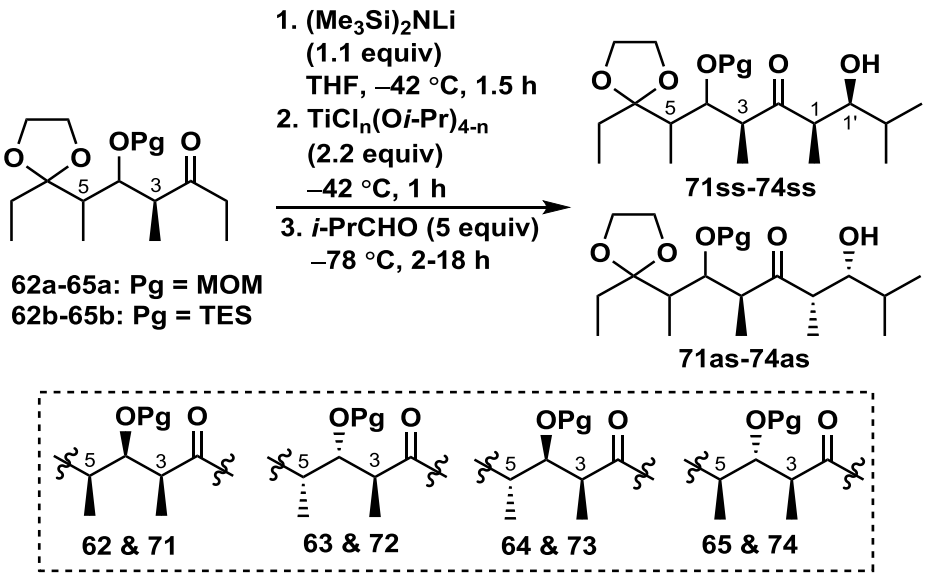
entry	ketone	enolization[a] (*Z*:*E*)	as:ss:aa:sa (convn)[b,c]	(1,3-*syn*:1,3-*anti*)[d]	isolated yield[e]
1	**62a**	10:1	9:6:1:ND[g]; 95%	1.5:1	44 (21)
2	**62b**	10:1	8:4:1:ND[g]; 95%	2:1	42[f]
3	**63a**	15:1	1:3.5:ND[g]:ND[g]; 95%	1:3.5	70 (20)
4	**63b**	3:1	15:1:ND[g]:6; 90%	15:1	55 (5)
5	**64a**	20:1	1.5:1:ND[g]:ND[g]; 95%	1.5:1	53 (33)
6	**64b**	15:1	8:5:ND[g]:1; 95%	1.6:1	49 (28)
7	**65a**	20:1	8:1:ND[g]:ND[g]; 95%	8:1	77 (6)
8	**65b**	20:1	2.7:1:ND[g]:ND[g]; 90%	2.7:1	61 (18)

* Results presented in entries 3-8 (Table 2.5) were obtained by Kundu, D. and Biniaz, M.

[a]Determined by ^{1}H NMR of the crude enol ethers obtained by addition of TMSCl/Et_3N (3:1) to the enolate at −78 °C. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [d]Calculated from the ratio of 1,3-*syn* to 1,3-*anti* aldols of Li (*Z*)-enolates (i.e., the ratio of **ss** and **as** aldol adducts). [e]Isolated yield of the major 1,1′-*syn* aldol adduct (isolated yield of the minor 1,1′-*syn* aldol adduct in parentheses). [f]Lower yield due to difficult fractionation. [g]Not detected.

Based on the work reported by Ward *et al*.,[82, 84] Ti(IV) (*Z*)-enolates of ketones **62-64** were prepared by transmetallation from the corresponding Li (*Z*)-enolates that were prepared as above (*cf*. Table 2.5). Both Ti(O*i*-Pr)$_4$ or TiCl(O*i*-Pr)$_3$ were used in the transmetallation reaction. The Ti(IV) (*Z*)-enolates generated using freshly prepared $TiCl_n(O\textit{i}\text{-Pr})_{4-n}$ (n = 1 or 2) were found to be more reactive (as indicated by shorter aldol reaction time) and provided higher diastereoselectivities in aldol couplings with **70**. The results obtained with $TiCl_n(O\textit{i}\text{-Pr})_{4-n}$ (n = 1 or 2) reagents for the eight possible ketones are summarized in Table 2.6. In all cases, the 1,3-*syn*-1,1′-*syn* (**ss**) aldol was produced with good to excellent diastereoselectivities (≥9:1) with the 1,3-*anti*-1,1′-*syn* (**as**) adduct as the minor product. The aldol couplings of both (*Z*)-enol borinates and Ti(IV) (*Z*)-enolates of ketones **62-64** provided the 1,3-*syn*-1,1′-*syn* (**ss**) aldol as the major product. The diastereoselectivities varied widely for (*Z*)-enol borinates but Ti(IV) (*Z*)-enolates uniformly provided higher diastereoselectivities (≥9:1) for all eight ketones. Therefore, the later method can be used to selectively access 1,3-*syn*-1,1′-*syn* (**ss**) aldol adduct for any of the eight possible ketones.

Table 2.6. Aldol couplings of Ti(IV) (*Z*)-enolates of **62-65** with **70**.*



entry	ketone	enolization	ss:as (convn)[a,b]	(1,3-*syn*:1,3-*anti*)[c]	isolated yield[d]
1	**62a**	TiCl(O*i*-Pr)$_3$; 2 h	12:1; 90%	12:1	76 (5)
2	**62b**	TiCl(O*i*-Pr)$_3$; 3 h	15:1; 85%	15:1	71 (4)
3	**63a**	TiCl(O*i*-Pr)$_3$; 1.5 h	13:1; >95%	13:1	87 (7)
4	**63b**	TiCl(O*i*-Pr)$_3$; 1 h	>19:1; 95%	>19:1	86
5	**64a**	TiCl(O*i*-Pr)$_3$; 5 h	15:1; 90%	15:1	78 (5)
6	**64b**	TiCl(O*i*-Pr)$_3$; 4 h	13:1; 95%	13:1	81 (5)
7	**65a**	TiCl(O*i*-Pr)$_3$; 4 h	13:1; 90%	13:1	76 (5)
8[e,g]	**65b**	TiCl$_2$(O*i*-Pr)$_2$;[f] 3 h	9.2:1; 65%	9.2:1	55 (5)

* Results presented in entries 3-9 (Table 2.6) were obtained by Kundu, D. and Biniaz, M.

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Calculated from the ratio of 1,3-*syn* to 1,3-*anti* aldols of Ti(IV) (*Z*)-enolates. [d]Isolated yield of the major aldol adduct (isolated yield of the minor adduct in parentheses). [e]Enolization using 1.4 equiv of $(Me_3Si)_2NLi$ at −78 °C for 2 h. [f]Transmetallation at −78 °C for 2 h. [g]Enolization in presence of 1 equiv. of $(Me_3Si)_2NH$.

2.2.2.1. Structure determinations of 71-74

A total 29 of the 32 possible aldol adducts were isolated from the aldol couplings of the eight ketones **62-65** (Pg = MOM or TES) with isobutyraldehyde (**70**). All four aldol adducts were isolated from the aldol couplings of each of the four MOM protected ketones **62a-65a**. Therefore, it can be concluded that the relative configurations of the starting ketones are intact in the corresponding aldol adducts and the same relationship was assumed for the aldol adducts obtained from the TES protected ketones **62b-65b**. Hence, establishing the relative configurations between C-3, C-1 and C-1′ stereocenters will secure the overall structures of all 29 aldol adducts. The aldol couplings of **62a** and **62b** with isobutyraldehyde (**70**) provided all of the eight possible aldol adducts (**71**) (Figure 2.2). The structure determination of these aldol adducts are presented below. The structure determinations of aldol adducts (**72-74**) that were prepared by others are briefly summarized.

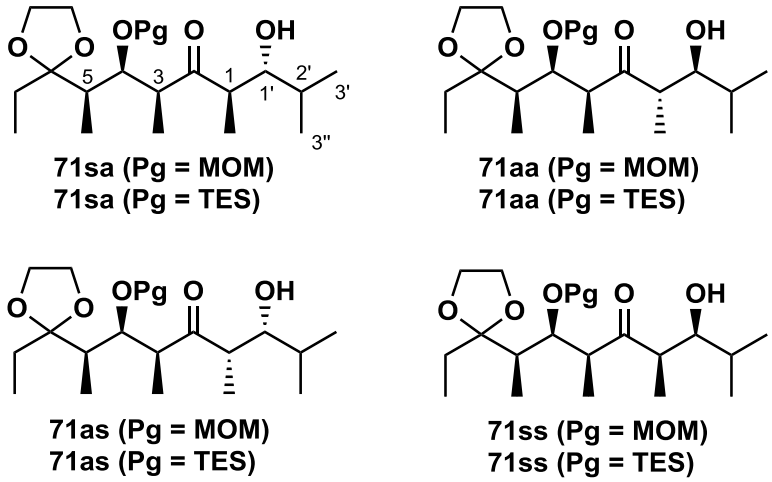


Figure 2.2. Eight possible aldol adducts obatined from the aldol couplings of **62** with **70**.

The 1,1′-relative configurations of 29 of the 32 possible aldol adducts were established based on $^3J_{H1\text{-}H1'}$ coupling constants[42, 116] and ^{13}C chemical shifts (δ_c) of the C1-Me groups.[117] As

shown in Table 2.7, the $^{3}J_{H1\text{-}H1'}$ coupling constants (J = 7-8.5 Hz, average = 7.4 Hz) and ^{13}C chemical shifts of the C1-Me groups (δ_c = 14.2-14.6 ppm, average = 14.4 ppm) were substantially larger for 1,1′-*anti* aldols (**71ss** and **71as**) than those (J = 1.5-2.5 Hz, average = 1.9 Hz; C1-Me δ_c = 8.7-9.3 ppm, average = 9.0 ppm) in the 1,1′-*syn* aldols (**71ss** and **71as**).

Table 2.7. Selected NMR data for aldol adducts **71**.

entry	aldol adduct	$^{3}J_{H1\text{-}H1'}$ (Hz)	$^{3}J_{H1'\text{-}H2'}$ (Hz)	δ_c (ppm) (CH_3C-1)	$\Delta\delta_c$ (C-1′/ CH_3C-1)[a]	$\Delta\delta_c$ (C-1/C-2′)[b]	$\Delta\delta_c$ (C-3′/C-3″)[c]
1	**71as** (Pg = MOM)	2.5	8.5	8.7	68.1	15.8	0.4
2	**71ss** (Pg = MOM)	1.5	9.5	9.3	66.8	16.0	1.0
3	**71sa** (Pg = MOM)	8.5	3	14.6	61.6	20.8	5.9
4	**71aa** (Pg = MOM)	7	4.5	14.2	64.7	17.7	4.5
5	**71as** (Pg = TES)	2	8	8.8	67.7	15.8	0.6
6	**71ss** (Pg = TES)	1.5	9.5	9.3	67.0	16.9	1.0
7	**71sa** (Pg = TES)	7	4.5	14.6	63.8	18.6	4.3
8	**71aa** (Pg = TES)	7	5	14.3	64.6	17.8	4.2

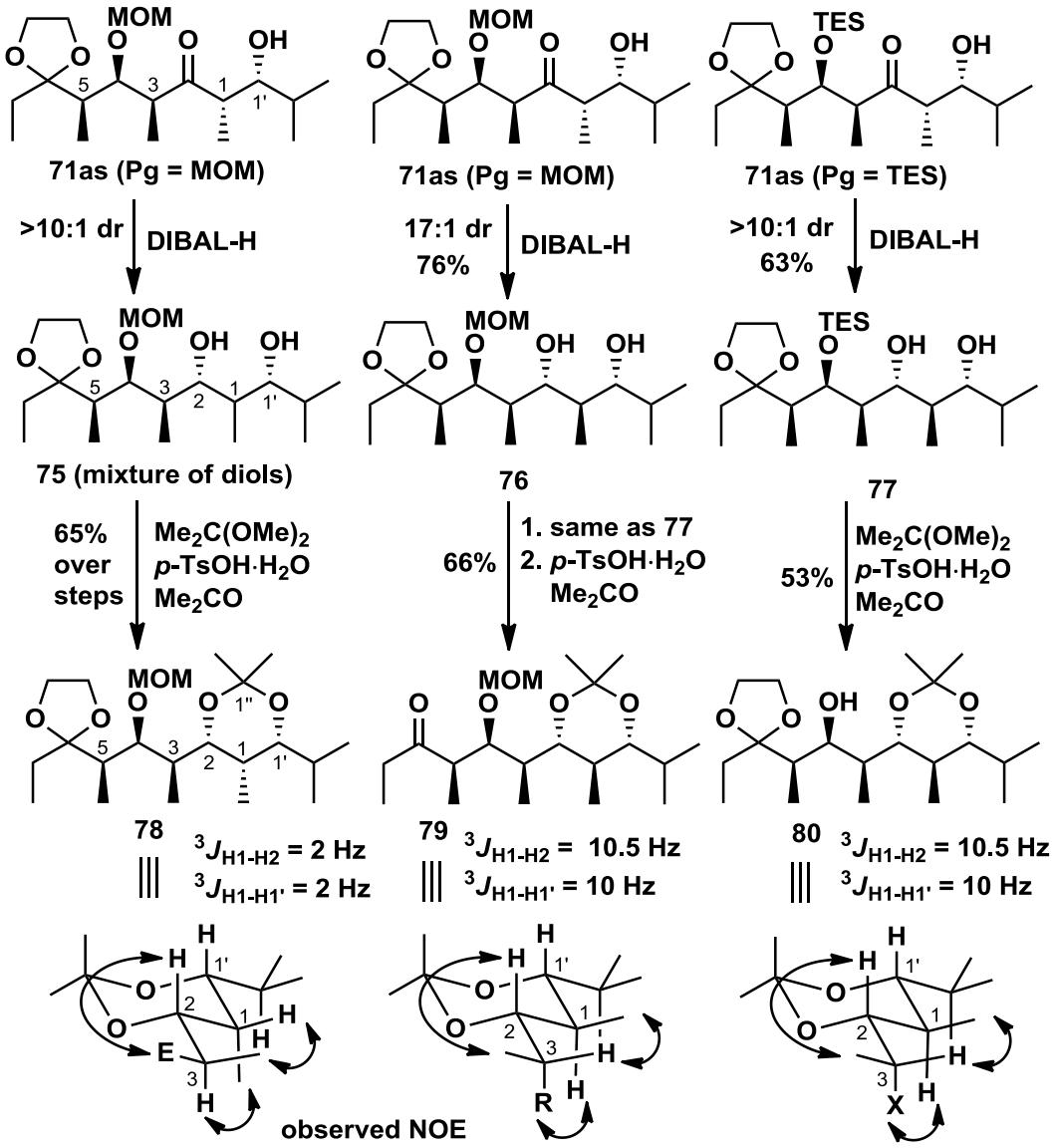
[a]Equal to (δ_c C1′) − (δ_c CH_3C-1) in ppm. [b]Equal to (δ_c C1) − (δ_c C-2′) in ppm. [c]Equal to (δ_c C3′) − (δ_c C-3″) in ppm.

Similar NMR trends were observed for the remaining 21 aldol adducts (**72**-**74**). In 13 cases, these assignments were confirmed by analyses of the coupling constants observed for the

corresponding acetonide derivatives of *syn* diols that were prepared by reduction of the aldol adducts (**71-74**). The acetonide derivatives of aldol adducts **71** are depicted in Scheme 2.4.

Having established the 1,1′-relative configurations of **71**, the next goal was to find out the 1,3-relative configurations of these aldols. One aldol adduct from each of the two possible pairs of 1,1′-*syn* (**71as**/**71ss** (Pg = MOM)) and 1,1′-*anti* aldols (**71sa**/**71aa** (Pg = MOM)) were selected for the corresponding acetonide formation. Both of these aldol adducts **71as** (Pg = MOM) and **71sa** (Pg = MOM) were reduced with DIBAL-H. Reduction of **71as** (Pg = MOM) afforded a >10:1 mixture of diols which was treated with $Me_2C(OMe)_2$ and *p*-TsOH·H_2O in acetone. Purification of the crude reaction mixture afforded acetonide **78** in 65% yield. In contrast, reduction of **71sa** (Pg = MOM) afforded 17:1 mixture of diols. Purification of the mixture provided 1′,2-*syn*-diol (**76**) in 76% yield. The 1′,2-*syn*-diol **76** was converted to acetonide **79** under the conditions similar to those described for **78**. Hydrolysis of the ketal group was observed under these conditions and a mixture of desired acetonide and **79** was formed. The mixture was treated with *p*-TsOH·H_2O in acetone to afford **79** in 66% yield. Acetonides **78** and **79** were used for NOE study. To differentiate the acetonides of 1′,2-*syn* diols from that of 1′,2-*anti* diols, ^{13}C NMR correlations were used, as described by Rychnovsky *et al*.[118] Such acetonide derivatives of 1′,2-*syn*-diols were expected to adopt a single chair confirmation and this property was essential to the analysis.

Scheme 2.4. Structure determinations of **71**.



The relative configurations of C-2, C-1 and C-1′ stereocenters of **78** (Scheme 2.4) obtained from aldol **71as** (Pg = MOM) were established based on the magnitudes of $^{3}J_{\text{H1-H2}}$ and $^{3}J_{\text{H1-H1′}}$ coupling constants that were consistently small (≤2 Hz) as expected for 1,2-*syn*-1,1′-*syn* acetonides. The 1,3-relative configuration of **71as** was secured by the following NOE correlations: HC-3↔H_3CC-1, H_3CC-3↔HC-1, HC-4↔HC-2 indicated with double headed arrows in Scheme 2.4. Similarly, the $^{3}J_{\text{H1-H2}}$ and $^{3}J_{\text{H2-H1′}}$ coupling constants (consistently high (≥10 Hz) for 1,2-*anti*-1,1′-*anti* acetonides) and HC-2↔H_3CC-3, HC-3↔H_3CC-1 and HC-1↔HC-4 NOE correlations observed for **79** confirmed the structure of the starting aldol **71sa** (Pg = MOM). Establishing the

1,3-relative configurations of one of the two possible aldols in each pair of 1,1′-*syn* (i.e., **71as** (Pg = MOM)) and 1,1′-*anti* (i.e., **71sa** (Pg = MOM)) aldols establishes the 1,3-relative configurations of the remaining aldol adducts **71ss** (Pg = MOM) and **71aa** (Pg = MOM). Similarly, the structures of 12 more MOM protected aldol adducts (prepared by others) were established by the formation acetonides and NOE correlations.* In each case, the assignments of 1,1′-relative configurations based on NMR data of the acetonides were consistent with that of the direct NMR based determinations.

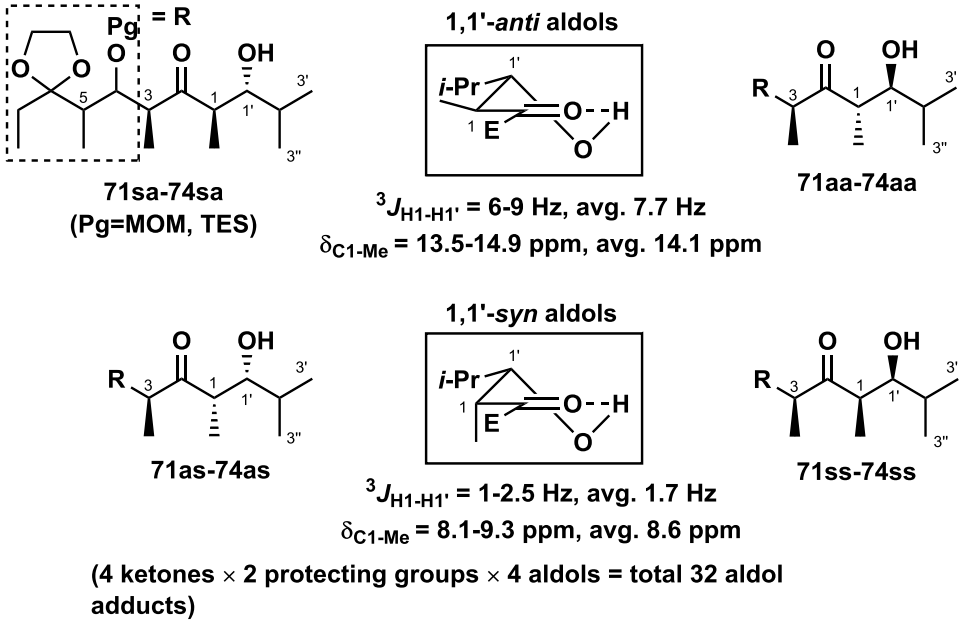


Figure 2.3. Determinations of 1,1′-relative configurations of aldols **71-74** by NMR.

Having established the relative configurations for the complete set of 16 diastereomers **71-74** (Pg = MOM), the next goal was to identify trends in their ^{1}H and ^{13}C NMR data which can be used to secure the structures of the related aldol adducts. Toward that end, each of the aldol adducts were analyzed carefully and clear trends were identified (Figure 2.3). In addition to the known criteria ($^{3}J_{H1\text{-}H1'}$ coupling constant[42, 116] and ^{13}C chemical shift[117] of the C1-Me group), the $^{3}J_{H1'\text{-}H2'}$ coupling constant and the difference in the ^{13}C chemical shifts of two diastereotopic methyl

* The acetonides were prepared and their NOE studies were performed by Kundu, D. and Biniaz, M.

groups at C-2′ (Δδc (C-3′/C-3″)) provided clear differentiation of 1,1′-*syn* and 1,1′-*anti* diastereomers. For example, the 1,1′-*syn* diastereomers had larger $^{3}J_{H1'\text{-}H2'}$ coupling constants and smaller Δδc (C-3′/C-3″) values whereas the corresponding 1,1′-*anti* diastereomers had smaller $^{3}J_{H1'\text{-}H2'}$ coupling constants and larger Δδc (C-3′/C-3″) values (compare entries 5 and 6 with entries 7 and 8, Table 2.7). The 1,1′-*syn* aldol adducts (**as** (Pg = TES) and **ss** (Pg = TES)) were distinguished from 1,1′-*anti* aldol adducts (**sa** (Pg = TES) and **aa** (Pg = TES)) by the clear trends observed in the difference of ^{13}C chemical shifts of C-1 and C-2′ (Δδc (C-1/C-2′)) and C-1′ and CH_3C-1 (Δδc (C-1′/CH_3C-1)). For instance, aldols with 1,3-*syn* relative configurations (i.e., **71ss** (Pg = TES) and (**71sa** (Pg = TES)) had higher Δδc (C-1/C-2′) and lower Δδc (C-1′/CH_3C-1) values (Table 2.7). In contrast, lower Δδc (C-1/C-2′) and higher Δδc (C-1′/CH_3C-1) values were observed for aldols having 1,3-*anti* relative configurations (i.e., **71as** (Pg = TES) and (**71aa** (Pg = TES)). These trends were consistent in the remaining 11 diastereomers **72-74** (Pg = TES) (not shown).

The structures of **71sa** (Pg = TES) and **71aa** (Pg = TES) could not be firmly established based on the above NMR trends because of the small differences in $^{3}J_{H1'\text{-}H2'}$, Δδc (C-1/C-2′), Δδc (C-1′/CH_3C-1) or ΔC-3″) values for the two diastereomers. To confirm the structures of **71sa** (Pg = TES) and **71aa** (Pg = TES), aldol **71sa** (Pg = TES) was converted to the corresponding acetonide **80** (Scheme 2.4). DIBAL-H reduction of **71sa** (Pg = TES) provided a >10:1 mixture of diols which was purified to afford 1′,2-*syn* diol **77** in 63% yield. Diol **77** was converted to acetonide **80** by treatment with $Me_2C(OMe)_2$ and *p*-TsOH·H_2O in acetone. Deprotection of the TES group was observed under these conditions and acetonide **80** was isolated in 53% yield. The $^{3}J_{H1\text{-}H2}$ and $^{3}J_{H1\text{-}H1'}$ coupling constants (J = ≥10 Hz) were consistent with 1,2-*anti*-1,1′-*anti* acetonide (**80**) and the NOE correlations (HC-2↔H_3CC-3, HC-3↔H_3CC-1 and HC-1↔HC-4) confirmed the 1,3-*syn* relative configuration of **71sa** (Pg = TES).

2.2.3. Aldol couplings of chiral aldehydes with enolates of chiral ketones

Having identified the reaction conditions that provided high diastereoface selectivities in the aldol couplings both of chiral ketones **62-65** with an achiral aldehyde and of chiral aldehydes **29** with an achiral enolate, the next goal was to perform the aldol couplings of **62-65** with **29** under similar reaction conditions.

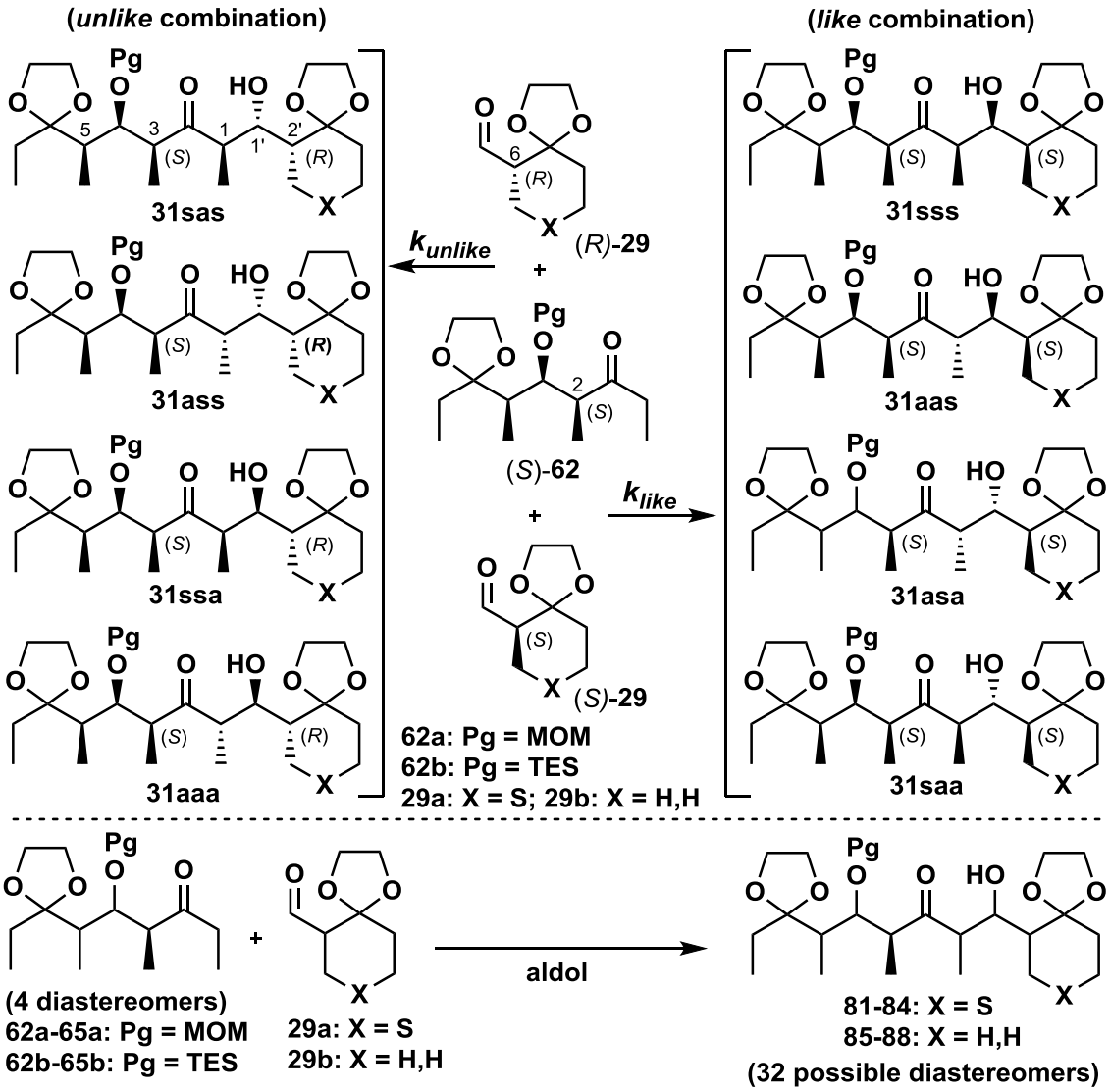


Figure 2.4. Aldol couplings of **62-65** and **29**.

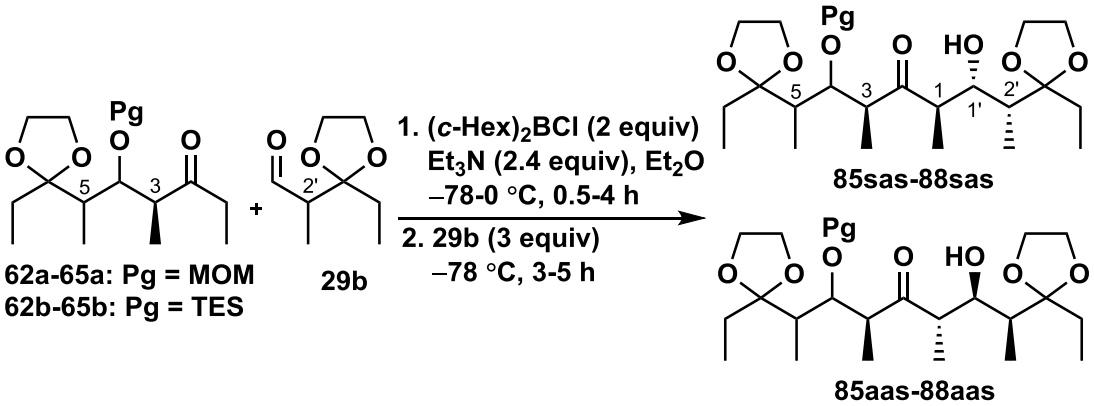
The aldol coupling of (*R*)-**29** with enolates of (*S*)-**29** can form up to four diastereomers: **31sas**, **31ass**, **31ssa** and **31aaa** (Figure 2.4). If one or both the reactants are racemic, the aldol coupling can form up to eight diastereomers: four each from the *like* (**31sss**, **31aas**, **31asa**, **31saa**) and the *unlike* (**31sas**, **31ass**, **31ssa**, **31aaa**) combinations of reacting enantiomers. As a result, there are 64 possible diastereomers from the aldol couplings of eight ketones **62-65** with **29**. The MKEs of such aldol couplings can be measured from the ratio of diastereomers resulting from the *like* and the *unlike* reactions. Aldol coupling which proceed with high level of MKE (ca. >10:1) are expected to proceed with useful levels of KR if one of the reactants is non-racemic and the corresponding aldol products will also be non-racemic. To identify suitable reactants and reaction

conditions, initial aldol couplings were performed with racemic **29** and racemic **62-65** and the results are presented below.

2.2.3.1. Aldol couplings of racemic 29 with enolates of racemic 62-65 (MKE)

Aldol couplings of (*E*)-enol borinates of **62-65** with isobutyraldehyde (**70**) provided 1,3-*syn*-1,1′-*anti* (**sa**) aldols as the predominant products with good to excellent diastereoselectivities (*cf.* Table 2.2). Similar reactions of (*E*)-enol dicyclohexylborinate of 3-pentanone (**58**) with aldehydes **29a** and **29b** provided 1,1′-*anti*-1′,2′-*syn* (**as**) aldols as the exclusive product (*cf.* entries 1and 2, Table 2.1). According to the multiplicativity rule, the aldol coupling of (*E*)-enol borinates of **62-65** with **29** should provide the 1,3-*syn*-1,1′-*anti*-1′,2′-*syn* (**sas**) diastereomer with high diastereoselectivities. To test this hypothesis, (*E*)-enol borinates of **62a** and **62b** were generated under the previously optimized conditions (*cf.* Table 2.2) and treated with **29b** at −78 °C (entries 1 and 2, Table 2.8). After 3 h, standard oxidative work up provided the crude mixtures whose ^{1}H NMR showed the presence of **85sas** as the only detectable diastereomer.

Table 2.8. Aldol couplings of (*E*)-enol borinates of **62-65** with **29b**.*



entry	ketone	enolization	sas:aas (convn)[a,b]	MKE[c]	isolated yield (%)[d]
1	**62a**	0 °C, 2 h	>19:1; 80%	>19:1	73
2	**62b**	0 °C, 0.5 h	>19:1; 95%	>19:1	93
3	**63a**	−78 °C, 2 h	>19:1; 85%	>19:1	79
4	**63b**	−78 °C, 4 h	>19:1; 85%	>19:1	77
5	**64a**	−78 °C, 4 h	>19:1; 95%	>19:1	87
6	**64b**	−78 °C, 4 h	>19:1; 80%	>19:1	73
7	**65a**	−78 °C, 5 h	7:1; 85%	7:1	81
8	**65b**	−78 °C, 5 h	>19:1; 58%	>19:1	51

* Results presented in entries 3-8 (Table 2.8) were obtained by Kundu, D. and Biniaz, M.

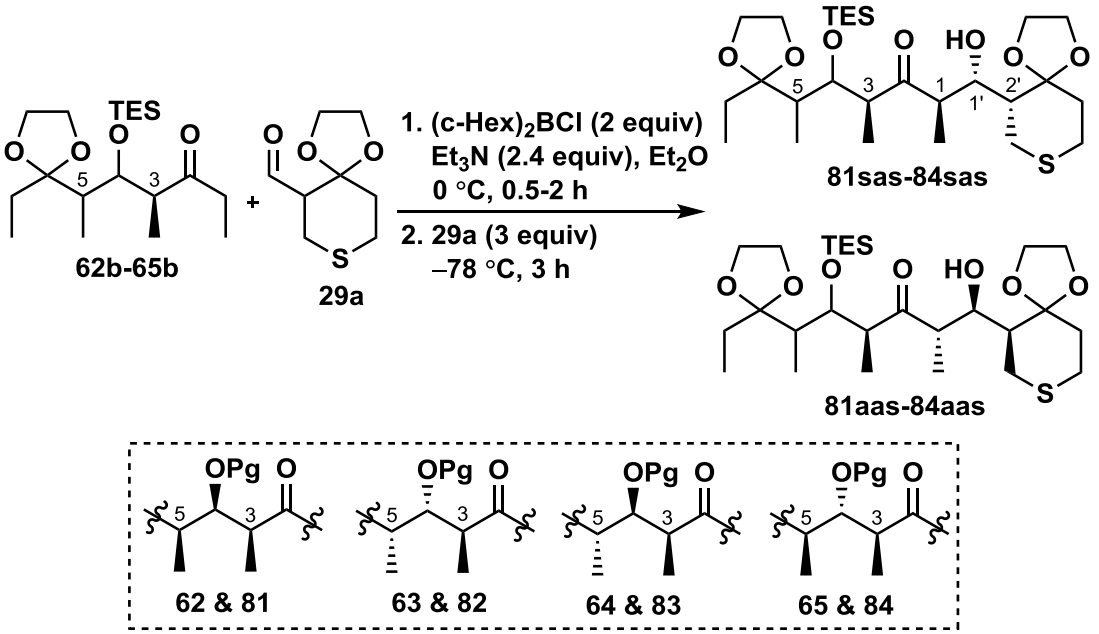
[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Represents k_{unlike} vs. k_{like} reactions of (*E*)-enol borinates. [d]Isolated yield of the major aldol adduct.

Though the diastereoselectivity (3:1) of aldol coupling of the (*E*)-enol borinate of **62b** with isobutyraldehyde (**70**) was significantly lower (*cf*. entry 2, Table 2), similar aldol coupling with **29b** proceeded with excellent diastereoselectivity (entry 2, Table 2.8). Similar to **62**, the aldol couplings of (*E*)-enol borinates of **63-65** with **29b** (entries 3-8) were also investigated (entries 3-8)* and the 1,3-*syn*-1,1′-*anti*-1′,2′-*syn* (**sas**) diastereomers were obtained as the major products with good to excellent diastereoselectivities. The results tabulated in Table 2.8 demonstrate that the *unlike* combination of reactant enantiomers is the 'matched' reaction.

The aldol couplings of **29a** with (*E*)-enol borinates of **62-65** (Pg = TES) were also investigated and the results are summarized in Table 2.9. The enolizations of **63b-65b** following the conditions mentioned in Table 2 or Table 2.8 followed by aldol couplings with **29a** provided extremely low conversion toward aldol adducts. Hence, the reaction conditions shown in Table 2.9 were used for this investigation. Under these conditions, the aldol couplings of three of the four ketones provided the corresponding aldol adducts with high conversions (entries 1-3) whereas extremely low conversion (~20%) was obtained in case of **65b**. Consequently, the (*E*)-enol borinate of **65b** was generated by transmetallation of the corresponding Li (*Z*)-enolate.[119-120] In accordance with the prediction of the multiplicativity rule, each of the reactions selectively provided the **sas** diastereomer (one of eight possibilities) with high levels of MKE. Each of the aldol products were isolated in good to excellent yields and were used in isomerization study which will be discussed in section 2.3.4.

* Reactions were performed by Kundu, D. and Biniaz, M.

Table 2.9. Aldol couplings of (*E*)-enol borinates of **62b-65b** with **29a**.



entry	ketone	enolization	sas:aas (convn)[a,b]	MKE[c]	isolated yield (%)[d]
1	**62b**	0 °C, 0.5 h	>19:1; 84%	>19:1	73
2	**63b**	0 °C, 0.5 h	>19:1; >95%	>19:1	94
3	**64b**	0 °C, 2 h	>19:1; >95%	>19:1	89
4[e]	**65b**	−42 °C, 1.5 h −42 °C, 1 h	>19:1; 86%	>19:1	82

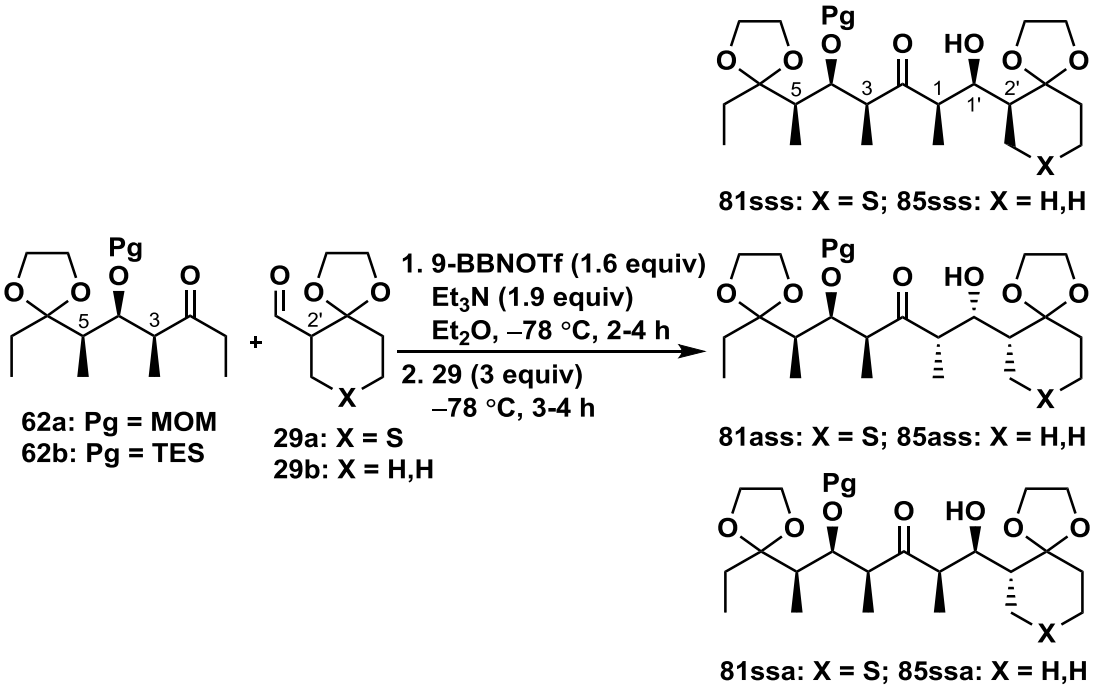
[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Represents k_{unlike} vs. k_{ike} for reactions of (*E*)-enol borinates. [d]Isolated yield of the major aldol adduct. [e]1.4 equiv LiHMDS was used and the transmetallation was performed with 2.2 equiv of (*c*-Hex)$_2$BCl.

The **sas** aldol adducts in Tables 2.8-2.9 have 1,3-*syn*-1,1′-*anti*-1′,2′-*syn* (sas) relative configurations (see section 2.2.4.) and resulted from the *unlike* combination of reactant enantiomers (i.e., (*S*)-enantiomers of **62-65** with the (*R*)-enantiomer of **29**). In contrast, the *like* combinations were favored in related aldol couplings of the (*E*)-enol borinates of corresponding cyclic (thiopyran) analogues of ketones **62-65** and **29a** (*cf.* Scheme 1.1) and the 1,3-*anti*-1,1′-*anti*-1′,2′-*syn* (**aas**) diastereomers were obtained as the predominant products.[84] This is because the

diastereoface selectivities of aldehyde additions to (*E*)-enol dicyclohexylborinates of acyclic ketones **62-65** were selective toward 1,3-*syn* aldols whereas similar aldol couplings of corresponding cyclic (thiopyran) ketones were selective toward 1,3-*anti* aldols. Detection of a single isomer of the eight possible diastereomers suggests that the rate constant for the *unlike* reaction (k_{unlike}) must be significantly higher (>19 fold) than that of the *like* reaction (k_{like}) (i.e., MKE = k_{unlike} / k_{like} = >19:1). Accordingly, these reactions should proceed with KR under these conditions if one of the reactants is non-racemic (see Table 2.14).

The aldol couplings of (*Z*)-enol borinates of **62a** and **62b** with **29** were also investigated. The (*Z*)-enol borinates of **62** were generated under the previously optimized conditions (*cf.* Table 2.3) and then treated with **29**. The results of this investigation are presented in Table 2.10. Low diastereoselectivities were obtained in aldol couplings of **29b** with (*Z*)-enol borinates of **62** (entries 1 and 2). The **sss** diastereomer was formed was the major product and the **ssa** diastereomer was found to be the minor product along with **ass** and **sas** diastereomers (see section 2.2.4.). Based on the diastereoface selectivity observed in enolate addition to **29b** (entry 3, Table 1), it was suspected that **ssa** diastereomer resulted from the non-Felkin addition of the (*Z*)-enol borinate to **29b**. The reason for the formation of **ass** and **sas** was not obvious at this point. It was expected that the diastereoselectivity of the aldol couplings would be increased by using **29a** that is known[81] to be highly Felkin selective in aldol couplings with related ketones (*cf.* Scheme 1.1). Toward that end, aldol couplings of (*Z*)-enol borinates of **62** with **29a** were performed (entries 3 and 4). Indeed, improved diastereoselectivities were obtained in the aldol couplings of **29a** with (*Z*)-enol borinates of both **62a** and **62b**. Each of these reactions proceeded with moderate MKE (4.8-6:1). Thus, the aldol coupling of **29a** with (*Z*)-enol borinate of **(+)-62b** was performed (KR) and the corresponding aldol adduct **(+)-81sss** was isolated in 57% yield (entry 5).

Table 2.10. Aldol couplings of (*Z*)-enol borinates of **62-65** with **29**.



entry	ketone	aldehyde	sss:ssa:ass:sas (convn)[a,b]	MKE[c]	isolated yield (%)[d]
1	**62a**	**29b**	6.7:3:1.7:1; 85%	1.3:1	75
2	**62b**	**29b**	15:5:1:2; 78%	1.9:1	58
3	**62a**	**29a**	(6:1:ND[f]:ND[f])[e]; 83%	6:1	61
4	**62b**	**29a**	21:1.3:2:1; 75%	4.8:1	50
5	**(+)-62b** (99% *ee*)	**29a**	12.8:1:1.5:1.3; 88%	(3.3:1)[g]	57

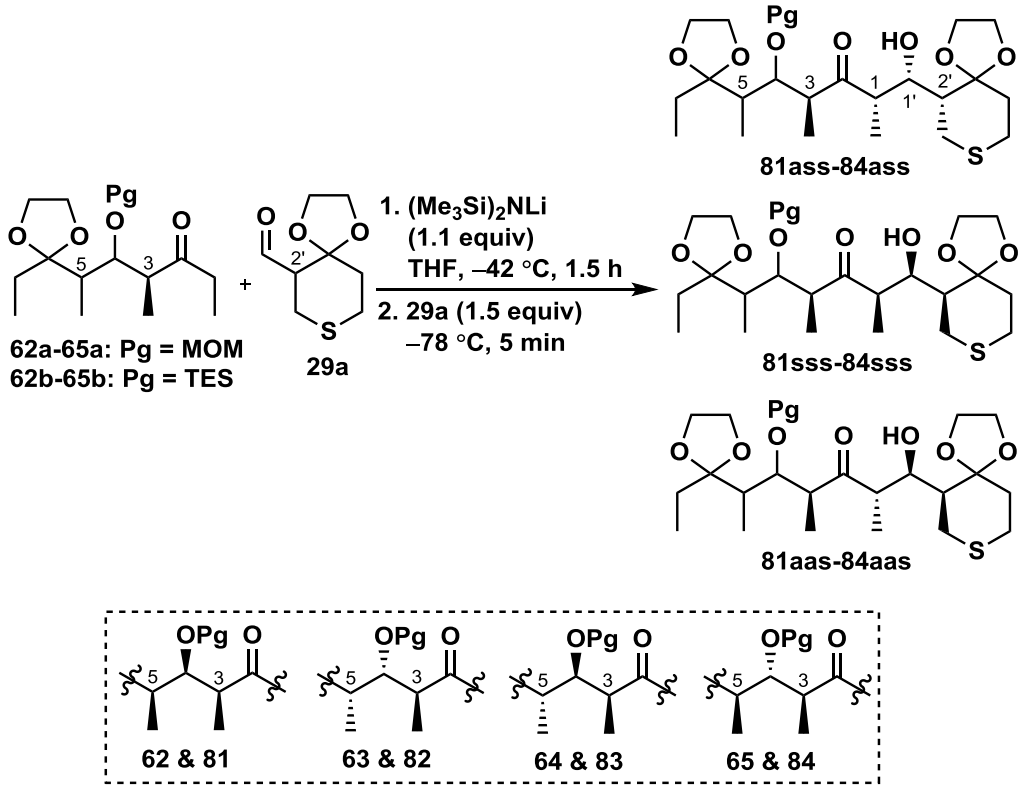
[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Represents k_{unlike} vs. k_{like} reactions of (*Z*)-enol borinate. [d]Isolated yield of the major aldol adduct. [e]Also contains two unidentified aldol adducts (~5% each). [f]Not detected. [g]Represents the ratio of *like*:*unlike* products with **sas** accounted for.

The diastereoface selectivities of additions of isobutyraldehyde (**70**) to the Li (*Z*)-enolates of **62-65** were low and 1,3-*anti*-1,1′-*syn* (**as**) aldols were obtained as the major products in most cases (*cf*. Table 2.5). Although the aldol couplings of **29** with Li (*Z*)-enolate of 3-pentanone

(**58**) provided low diastereoselectivities (1.3-2:1; entries 7 and 8, Table 2.1), only 1′,2′-*syn* (Felkin) aldols were obtained. Therefore, the aldol couplings of Li (*Z*)-enolates of **62-65** with **29** should provide 1,3-*anti*-1,1′-*syn*-1′,2′-*syn* (**ass**) diastereomers as the major products (see section 2.2.4.). To test this hypothesis, the aldol couplings of the Li (*Z*)-enolates of **62-65** with **29a** were investigated. The Li (*Z*)-enolates of **62-65** were generated using previously optimized conditions (*cf*. Table 2.5) and subsequent aldol couplings were performed with **29a**. The results are summarized in Table 2.11.

Up to three aldol diastereomers were detected in the ^{1}H NMR spectra of the crude reaction mixtures and the **ass** diastereomer was the major product in all cases (Table 2.11). The **sss** diastereomer was detected as the minor product, sometimes accompanied with the **sas** diastereomer (entries 4 and 6) or an unknown adduct (entries 1-3). The calculated ratios of 1,1′-*syn* and 1,1′-*anti* aldols were consistent with previously determined *Z*:*E* ratios of the Li enolates if the unknown compound was assumed to be a 1,1′-*anti* aldol. Moreover, the ^{1}H and ^{13}C NMR analysis of a 7:1 mixture of **ass** and an unknown compound (entry 2) suggested the unknown compound is the **aas** diastereomer presumably arising from the Li (*E*)-enolate. Therefore, the unknown compound detected in the crude reaction mixtures of other ketones were assumed to be the **aas** diastereomers. Because the **aas** and **sas** diastereomers presumably resulted from the Li (*E*)-enolates and their formation might be avoided by using diastereomerically pure Li (*Z*)-enolates, these isomers were not considered in the discussion of the diastereoselectivities of the Li (*Z*)-enolates. The aldol couplings of each of the eight possible ketones proceeded with low (1.2-2.5:1) to moderate (4.5-5.5:1) MKEs. Each of the *unlike* and the *like* reactions provided one of the four possible diastereomers, predominantly. Therefore, both the *unlike* and the *like* reactions were highly diastereoselective. Hence, high diastereoselectivities are expected in aldol couplings of Li (*Z*)-enolates of enantiopure **62-65** with enantiopure **29a**.

Table 2.11. Aldol couplings of Li (*Z*)-enolates of **62-65** with **29a**.



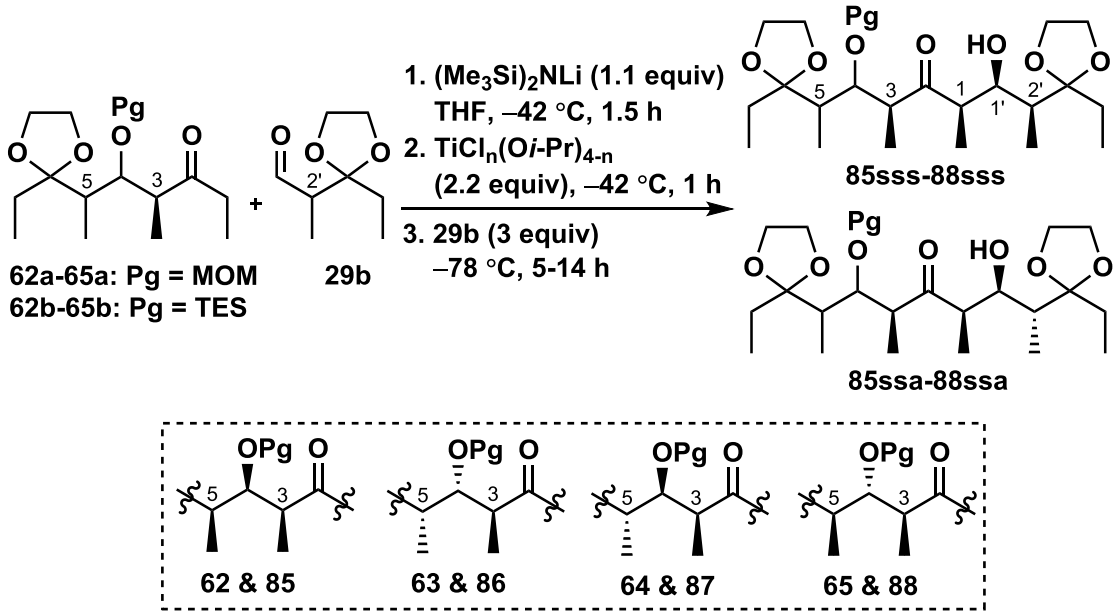
entry	ketone	enolate[a] (*Z*:*E*)	ass:sss:unknown[i] (convn)[b,c]	MKE[d]	isolated yield (%)[e]
1	**62a**	10:1	6:3.3:1; 84%	1.8:1	43(27)
2	**62b**	10:1	8.4:2.3:1; 85%	3.6:1	64[j](16)
3	**63a**	15:1	10:4:1; 83%	2.5:1	54 (22)
4	**63b**	3:1	4:1:1.5[g]; 88%	4:1	44(13)
5	**64a**	20:1	1.3:1:ND[h]; 79%	1.3:1	44(31)
6	**64b**	15:1	5:5:1[g]; 70%	1:1	27(23)
7[f]	**65a**	20:1	4.5:1:ND[h]; 85%	4.5:1	63(20[k])
8[f]	**65b**	20:1	2.4:1:ND[h]; 94%	2.4:1	64(25)

[a]Taken from Table 2.5. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [d]Represents k_{unlike} vs. k_{like} reaction of Li (*Z*)-enolates (i.e., only 1,1′-*syn* products were considered and unknown not considered). [e]Isolated yield of the major aldol adduct (isolated yield of minor 1,1′-*syn* adduct in parentheses). [f]Used 1.4 equiv LiHMDS and 2 equiv of **29a**. [g]Represents **sas** diastereomer. [h]Not detected. [i]Represents an unknown compound — presumably **aas** (see text). [j]Yield of a 7:1 mixture of **81ass** and **81aas**. [k]Yield of a 1.7:1 mixture of **84sss** and **84ass**.

Promising results were obtained from the aldol couplings of Ti(IV) (*Z*)-enolates of **62-65** with isobutyraldehyde (**70**) (*cf*. Table 2.6). High diastereoface selectivities (≥9.2:1 dr) were obtained for all eight possible ketones and 1,3-*syn*-1,1′-*syn* (**ss**) aldols were the predominant products. On the other hand, low diastereoface selectivity (3:1) was obtained from the aldol coupling of **29b** with Ti(IV) (*Z*)-enolate of 3-pentanone (**58**) and the ^{1}H NMR showed the presence of both 1′,2′-*syn* (Felkin) and 1′,2′-*anti* (non-Felkin) aldols were detected (entry 9, Table 2.1). In contrast, similar aldol coupling with **29a** provided 1′,2′-*syn* (Felkin) aldols with good diastereoselectivity (entry 10, Table 2.1). Therefore, the aldol couplings of Ti(IV) (*Z*)-enolates of **62-65** should provide 1,3-*syn*-1,1′-*syn*-1′,2′-*syn* (**sss**) aldols in moderate diastereoselectivities with **29b** and improved diastereoselectivities with **29a**, according to the multiplicativity rule. To test this hypothesis, aldol couplings of Ti(IV) (*Z*)-enolates of **62-65** with **29b** were performed and the results are summarized in Table 2.12.*

* Reactions of **63-65** were performed by Kundu, D. and Biniaz, M.

Table 2.12. Aldol couplings of Ti(IV) (*Z*)-enolates of **62-65** with **29b**.*



entry	ketone	$TiCl_n(Oi\text{-}Pr)_{4-n}$	sss:ssa (convn)[a,b]	MKE[c]	isolated yield[d](%)
1	**62a**	$TiCl(Oi\text{-}Pr)_3$	5:1; 85%	5:1	81
2	**62b**	$TiCl(Oi\text{-}Pr)_3$	10:2:1[h]; 81%	3.3:1	81
3	**62b**	$Ti(Oi\text{-}Pr)_4$	9.8:1.7:1[h]; 88%	3.6:1	72
4	**63a**	$TiCl(Oi\text{-}Pr)_3$	6:1; 90%	6:1	59[e]
5	**63b**	$TiCl(Oi\text{-}Pr)_3$	12:1; 80%	12:1	74
6	**64a**	$TiCl(Oi\text{-}Pr)_3$	6:1; 85%	6:1	74
7	**64b**	$TiCl(Oi\text{-}Pr)_3$	6:1; 80%	6:1	65[e]
8[f]	**65a**	$TiCl(Oi\text{-}Pr)_3$	5:1; 85%	5:1	69[e]
9[f,g]	**65b**	$TiCl_2(Oi\text{-}Pr)_2$	5:1:1.5[h]; 58%	2:1	59

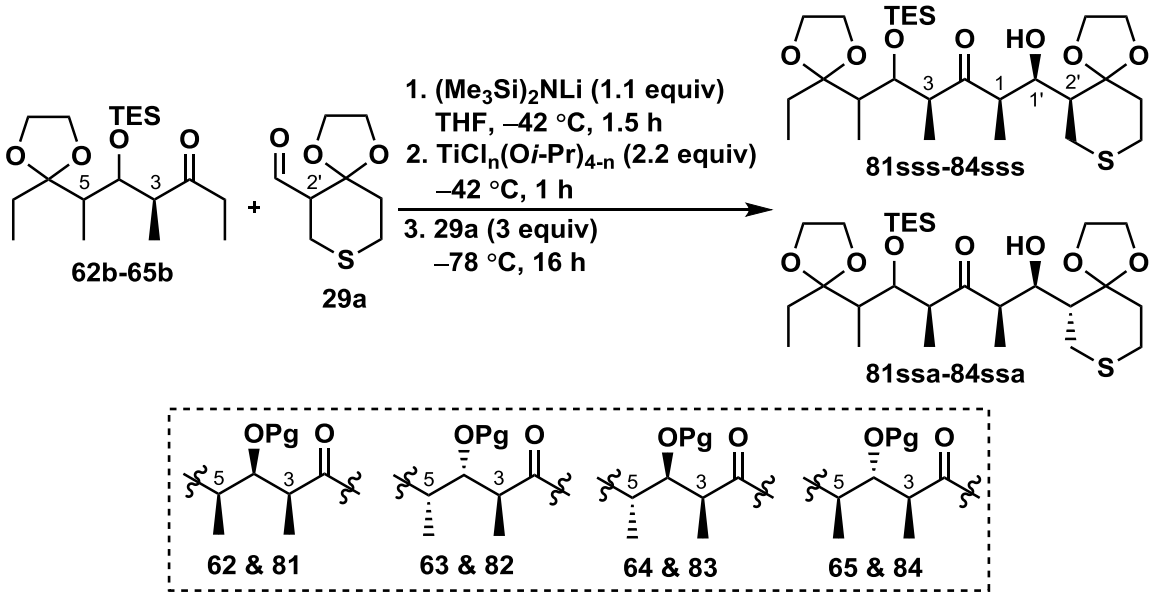
* Results presented in entries 3-8 (Table 2.12) were obtained by Kundu, D. and Biniaz, M.

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Represents k_{unlike} vs. k_{like} reactions of Ti (IV) (*Z*)-enolates (i.e., only 1,1′-*syn* products were considered). [d]Isolated yield of mixture of aldol adducts. [e]Isolated yield of the major aldol adduct. [f]1.4 equiv $(Me_3Si)_2NLi$ was used. [g]Enolization in presence of 1 equiv of added $(Me_3Si)_2NH$. [h]Represents **ass** diastereomer.

The Ti(IV) (*Z*)-enolates of **62-65** were generated under the previously optimized conditions and then treated **29b** at −78 °C. Similar to (*Z*)-enol borinates, these aldol couplings provided the **sss** diastereomers as the major products and the **ssa** diastereomers as the minor products (Table 2.12). The **ssa** diastereomer resulted from the "mismatched" reaction that is competitive (i.e., low MKE), consistent with the reaction of **29b** with Ti(IV) (*Z*)-enolate of 3-pentanone (**58**). The aldol coupling of **29b** with Ti(IV) "ate" (*Z*)-enolate of **62b** proceeded with low diastereoselectivity (entry 3, Table 2.12). As shown in Table 2.12, the aldol couplings of Ti(IV) (*Z*)-enolates of **62-65** with **29b** proceeded with low to moderate MKEs. Notably, the **sss** and **ssa** diastereomers resulted from separate reactions (*like* and *unlike*), each reaction being highly diastereoselective. Therefore, the aldol couplings of Ti(IV) (*Z*)-enolates of enantiopure **62-65** with enantiopure **29b** should proceed with high diastereoselectivities.

Aldol couplings of Ti(IV) (*Z*)-enolates of **62b-65b** and **29a** were also investigated and the results are summarized in Table 2.13. Superior results were obtained when $TiCl(O\textit{i}\text{-}Pr)_3$ was used in the aldol coupling of **62b** (entry 1) and $TiCl_2(O\textit{i}\text{-}Pr)_2$ was used in the aldol couplings of **63b-65b** (entries 2-4). Similar to **29b**, the aldol couplings of **29a** provided 1,3-*syn*-1,1′-*syn*-1′,2′-*syn* (**sss**) aldols as the predominant products which resulted from the *like* combination of reactant enantiomers whereas the two minor diastereomers **ass** and **ssa** resulted from the *unlike* combination of reactant enantiomers. The aldol couplings proceeded with moderate (5-6:1) to good (10:1) MKEs suggesting the *like* reaction (also "matched" in this case) is 5-10 fold faster than the *unlike* reaction. Therefore, a useful level of KR is expected in the aldol couplings of Ti(IV) (*Z*)-enolates of **62b-65b** with **29a** (when one of the reactants is non-racemic).

Table 2.13. Aldol couplings of Ti (IV) (*Z*)-enolates of **62-65** with **29a**.



entry	ketone	$TiCl_n(Oi\text{-}Pr)_{4-n}$	sss:ass:ssa:sas:unknown[c] (convn)[a,b]	MKE[d]	yield[e] (%)
1	**62b**	$TiCl(Oi\text{-}Pr)_3$	10:1: ND[h]:ND[h]:1[i]; 87%	10:1	61
2[f]	**63b**	$TiCl_2(Oi\text{-}Pr)_2$	14:1.3:1:1.4:ND[h]; 89%	6:1	70
3[f]	**64b**	$TiCl_2(Oi\text{-}Pr)_2$	25:ND[h]:2.5:1.5:1; 80%	10:1	64
4[f,g]	**65b**	$TiCl_2(Oi\text{-}Pr)_2$	11:1:ND[h]:1:1.5; 79%	11:1	58

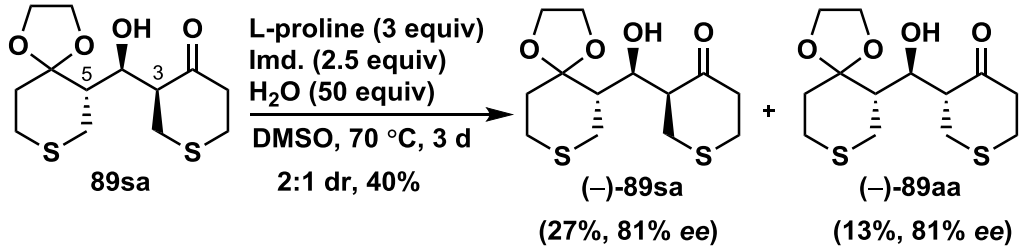
[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Tentatively assigned as **aas**. [d]Represents k_{unlike} vs. k_{ike} reactions of Ti(IV) (*Z*)-enolates (i.e., only 1,1′-*syn* products were considered). [e]Isolated yield of the major diastereomer. [f]Enolization in presence of 1 equiv of added HMDS. [g]Used 1.4 equiv LiHMDS. [h]Not detected. [i]Represents **aas** diastereomer.

2.2.3.2. Aldol couplings of racemic 29a with enolates of non-racemic 62b-65b (KR)

The aldol couplings of (*E*)-enol borinates and Ti (IV) (*Z*)-enolates of **62-65** with **29a** proceeded with moderate to excellent MKE. According to multiplicativity rule, KR should be expected under these conditions if one of the reactants is non-racemic. To test this hypothesis, access to either non-racemic ketones **62-65** or non-racemic aldehydes **29** was crucial. Ward *et al*. have reported the preparation of **(+)-29a** or **(−)-29a** in moderate yield (50%) yield and high enantiopurity (>95% *ee*).[121] The main drawbacks of this method[121] are the use of extremely low

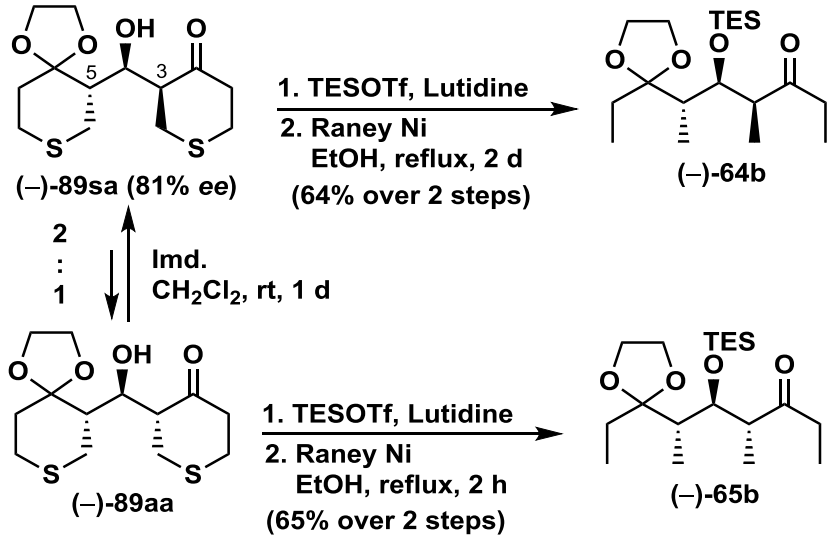
temperature (−100 °C) and multiple recrystallizations to obtain high enantiopurity of the product. Low yield and intricate operation made the preparations of **(+)-29a** or **(−)-29a** not scalable. In contrast, preparation of both **(−)-62b**[109] and **(+)-63b**[119] on multigram scale have previously been reported in the literature. Ketones **(+)-62b**[109] and **(+)-63b**[119] were prepared following the reported[109-110] procedures. Although the preparations of **(+)-89sa**[84] and **(+)-89aa**[84] have previously been reported, the method relies on the preparation of **(+)-29a**. A simpler method has been reported[122] in the Ward group that provides access to both **(−)-89sa** (22% yield, 92% *ee*) and **(−)-89aa** (10% yield, 93% *ee*). Following this reported procedure, aldols **(−)-89sa** and **(−)-89aa** were prepared albeit in lower enantiopurities (Scheme 2.5). No attempts were made to optimize these results.

Scheme 2.5. Preparation of **(−)-89sa** by enantioselective retroaldol reaction.



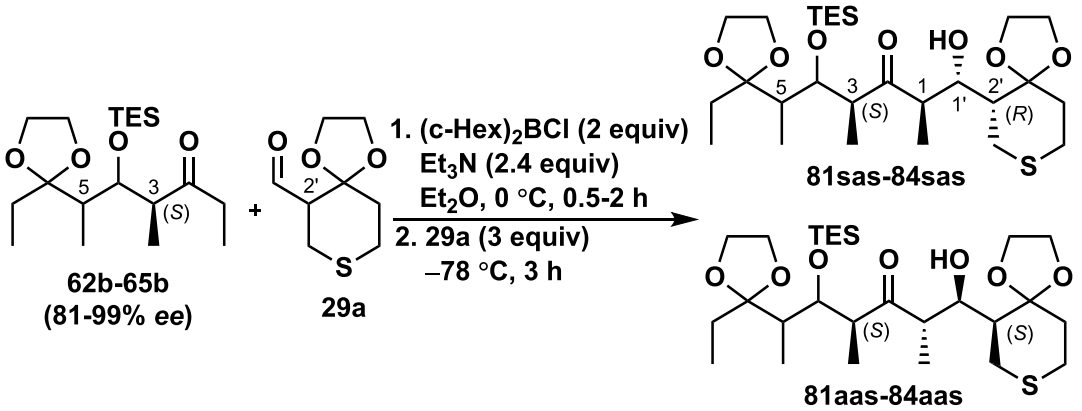
Though the above method provided (−)-**89sa** in reasonable yield (27%), the isolated yield for **(−)-89aa** was extremely low (13%). Isomerization of **89sa** to **89aa** via keto-enol tautomerization had previously been reported in literature.[123] Following the reported[123] procedure, **(−)-89sa** was isomerized to **(−)-89aa** to improve the overall yield for **(−)-89aa** (Scheme 2.6). As expected from the literature report,[123] a 2:1 mixture of **(−)-89sa** and **(−)-89aa** was obtained. Fractionation of the crude product provided **(−)-89sa** in 18% and **(−)-89aa** in 22% overall yields over two steps (based on **89sa**).

Scheme 2.6. Preparations of **(−)-89sa**, **(−)-64b**, and **(−)-65b**.



Following the reported[84] procedure, TES protections of **(−)-89sa** and **(−)-89aa** were performed. Desulfurizations of the crude products afforded **(−)-64b** and **(−)-65b** in 64% and 65% isolated yields, respectively. The enantiopurities of **(−)-64b** and **(−)-65b** were assumed to be same as **(−)-89sa** (i.e., 81% *ee*). The ^{1}H and ^{13}C NMR data of **(−)-64b** and **(−)-65b** closely matched those reported[124] for the previously established racemic **64b** and **65b**, respectively. Having access to all four enantioenriched ketones **(+)-62b**, **(+)-63b**, **(−)-64b** and **(−)-65b** in hand, the next goal was to study the KR in their reactions with **29a** via (*E*)-enol borinates and Ti(IV) (*Z*)-enolates.

Table 2.14. Aldol couplings of (*E*)-enol borinates of enantioenriched **62b-65b** with **29a**.

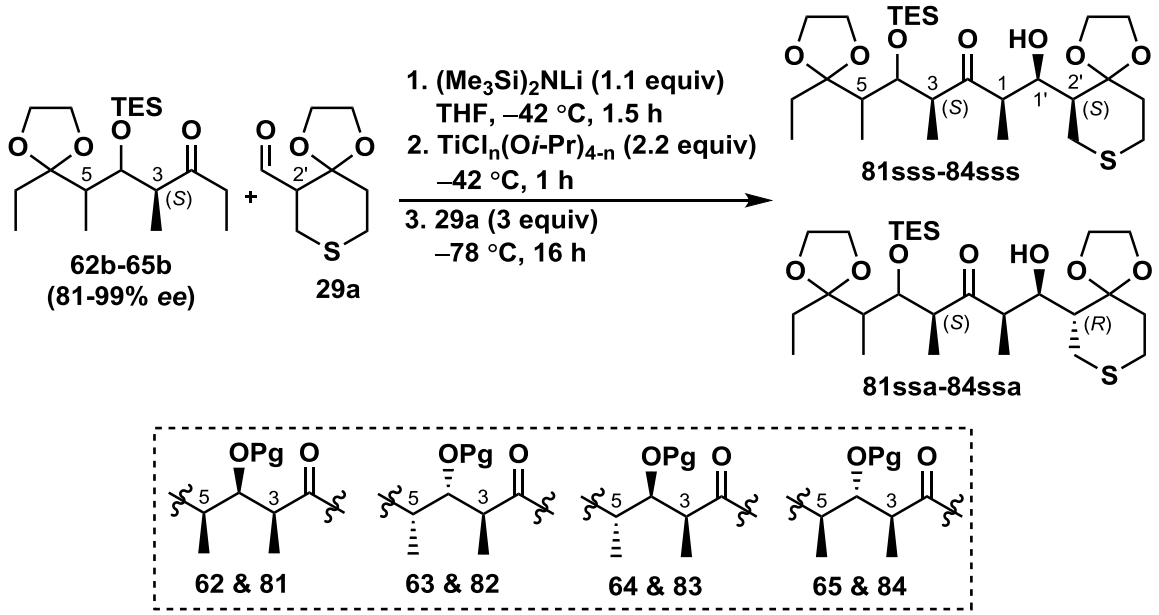


entry	ketone (% *ee*)	enolization	sas:aas (convn)[a,b]	selectivity of KR[c]	yield[d] (%)
1	**(+)-62b** (>98)	0 °C, 0.5 h	>19:1; >95%	>19:1	92
2	**(+)-63b** (>98)	0 °C, 0.5 h	>19:1; 84%	>19:1	80
3	**(−)-64b** (81)	0 °C, 2 h	>19:1; 86%	>19:1	81
4[e]	**(−)-65b** (81)	−42 °C, 1.5 h −42 °C, 1 h	>19:1; 80%	>19:1	76

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Estimated from the ratio of the sum of *unlike* (**sas**) and *like* (**aas**) products obtained from (*E*)-enolborinates. [d]Isolated yield of the major aldol adduct. [e]Used 1.4 equiv $(Me_3Si)_2NLi$ for enolization and 2.2 equiv of $(c\text{-Hex})_2BCl$ for transmetallation.

The aldol couplings of (*E*)-enol borinates of enantioenriched **62b-65b** with **29a** (Table 2.14) were performed under the conditions similar to those used for the corresponding racemic **62b-65b**. In all cases, the ^{1}H NMR of the crude reaction mixtures indicated the presence of a single aldol adduct **sas** (>19:1 dr). Each of the aldol adducts was isolated in good to excellent yield. The ^{1}H and ^{13}C NMR data for each of the enantioenriched **sas** aldol were indistinguishable from those for the corresponding racemic **sas** aldol.

Table 2.15. Aldol couplings of Ti(IV) (*Z*)-enolates of enantioenriched **62b-65b** with **29a**.



entry	ketone (% *ee*)	$TiCl_n(O\textit{i}\text{-}Pr)_{4-n}$	sss:ass:ssa:sas: unknown[c] (convn)[a,b]	like: unlike[d]	yield[e] (%)
1	**(+)-62b** (>98)	$TiCl(O\textit{i}\text{-}Pr)_3$	20:2:1:1.6:4[i]; 83%	6.7:1	66
2[f]	**(+)-63b** (>98)	$TiCl_2(O\textit{i}\text{-}Pr)_2$	8:1.2:1:1.5:ND[h]; 90%	3.6:1	60
3[f]	**(−)-64b** (81)	$TiCl_2(O\textit{i}\text{-}Pr)_2$	12:ND[h]:2:1:1.5; 89%	8:1	71
4[f,g]	**(−)-65b** (81)	$TiCl_2(O\textit{i}\text{-}Pr)_2$	6.7:1:ND[h]:1.7:2.4; 88%	6.7:1	55

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of aldol adducts to starting ketone in the crude reaction mixture by ^{1}H NMR. [c]Tentatively assigned as **aas**. [d]Estimated from the ratio of the sum of *like* (**sss**) and *unlike* (**ssa** and **ass**) products obtained from Ti(IV) (*Z*)-enolates (i.e., only 1,1′-*syn* products were considered). [e]Isolated yield of the major diastereomer. [f]Enolization in the presence of 1 equiv of added $(Me_3Si)_2NH$. [g]Used 1.4 equiv $(Me_3Si)_2NLi$. [h]Not detected. [i]Represents **aas** diastereomer.

The aldol couplings of Ti (IV) (*Z*)-enolates of enantioenriched **62b-65b** with **29a** were also examined under the conditions similar to those used for the corresponding racemic **62b-65b**. The results are summarized in Table 2.15. In all cases, the **sss** aldols were the major products. The ratios of *like*:*unlike* products obtained from the aldol couplings of Ti(IV) (*Z*)-enolates of enantioenriched ketones were lower than those obtained from similar aldol couplings of the corresponding racemic ketones. The ^{1}H and ^{13}C NMR data for each enantioenriched **sss** aldol were

indistinguishable from those for the corresponding racemic **sss** aldol. Significant increases in the amounts of **sas**, **aas** and **ssa** diastereomers were observed in aldol couplings of non-racemic ketones compared to those observed in the aldol couplings of corresponding racemic ketones (compare Tables 2.13 and 2.15). Although, the reason for these differences is unclear from the above experiments, the isomerization of Ti(IV) enolates/aldolates[125] cannot be ruled out. Further investigation is required to establish the origin of this observation.

2.2.4. Structure determination of 1′,2′-*syn* (Felkin) aldols 81-85

The aldol adducts depicted in Figure 2.5 were obtained from aldol reactions of **62-65** with **29**. The structure determinations of adducts synthesized by others are not presented here. The **sas** aldol diastereomers were the major products obtained from the reactions of (*E*)-enolborinates of **62b-65b** with **29**. The **sss** aldol diastereomers were the major products obtained from the reactions of (*Z*)-enolborinates and(or) Ti(IV) (*Z*)-enolates of **62-65** with **29**. The **ass** aldol diastereomers were the major products obtained from the reactions of Li (*Z*)-enolates of **62-65** with **29**. As with the structural assignments of the isobutyraldehyde aldol adducts (described in section 2.2.2.1.), it was assumed that the 3,4- and 4,5-relative configurations of aldol adducts shown in Figure 2.5 were identical to those of the corresponding starting ketones (**62-65**). Thus, establishing the 1,3-1,1′-1′,2′-relative configurations will secure the overall structures of the aldol adducts. There was no method available to directly assign the 1,3-1,1′-1′,2′-relative configurations of these aldol adducts. Therefore, two strategies were used to establish the structures of these aldol adducts. First, the design of the acyclic route to polypropionates (AR2P) allowed correlation of the aldol adducts of different ketones by derivatization — that is, the same aldol derivative can be accessed from aldol adducts from different ketones. Second, derivatives of some of the aldol adducts (e.g., **85sss**) were C_2 (axis of symmetry), or σ (sigma, plane of symmetry) symmetric (e.g., when Pg = H). The structures of these aldol adducts were established by taking advantage of these symmetry elements. The detailed structure elucidation of each of the aldol adducts depicted in Figure 2.5 are presented below.

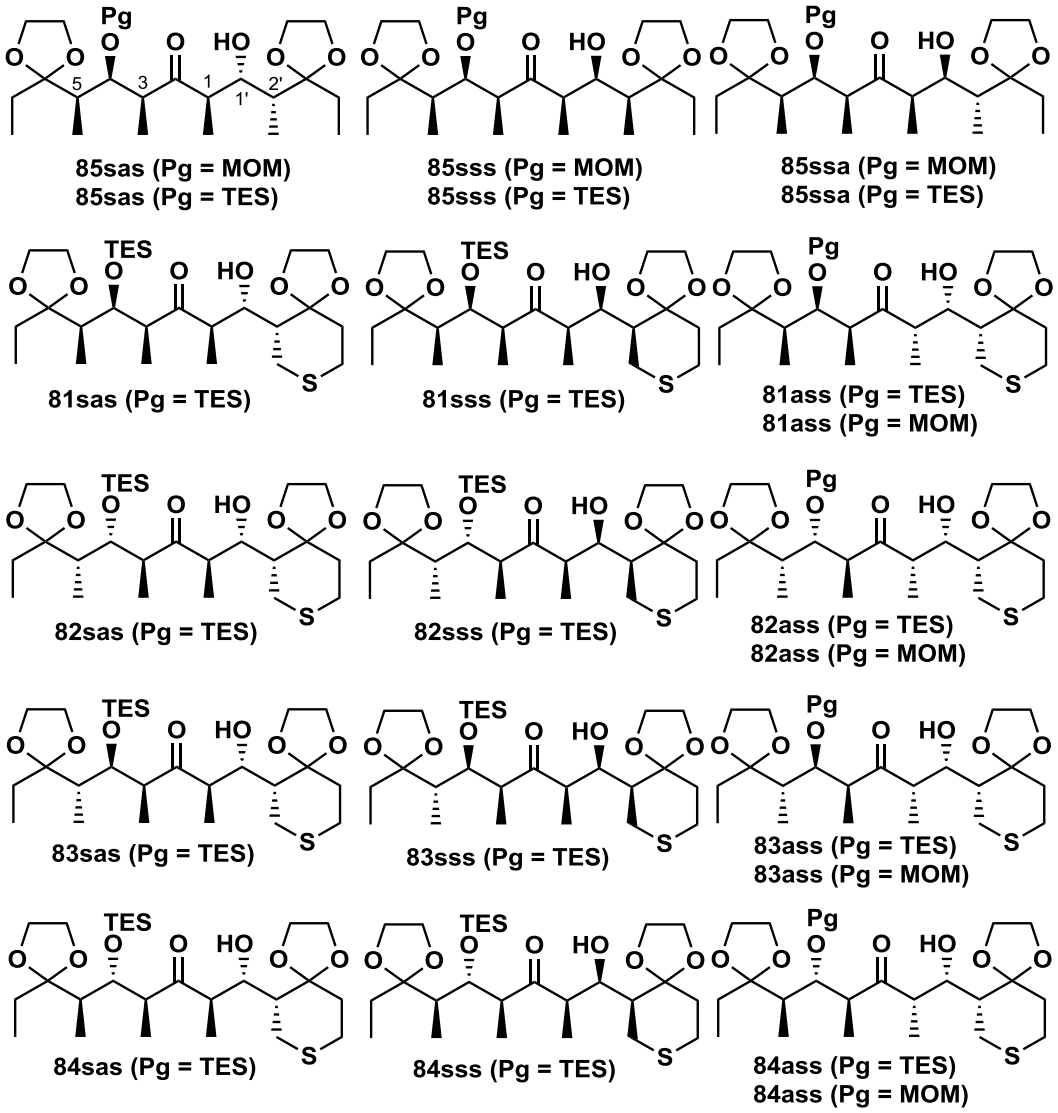


Figure 2.5. Aldol adducts obtained from the aldol couplings of **62b-65b** and **29**.*

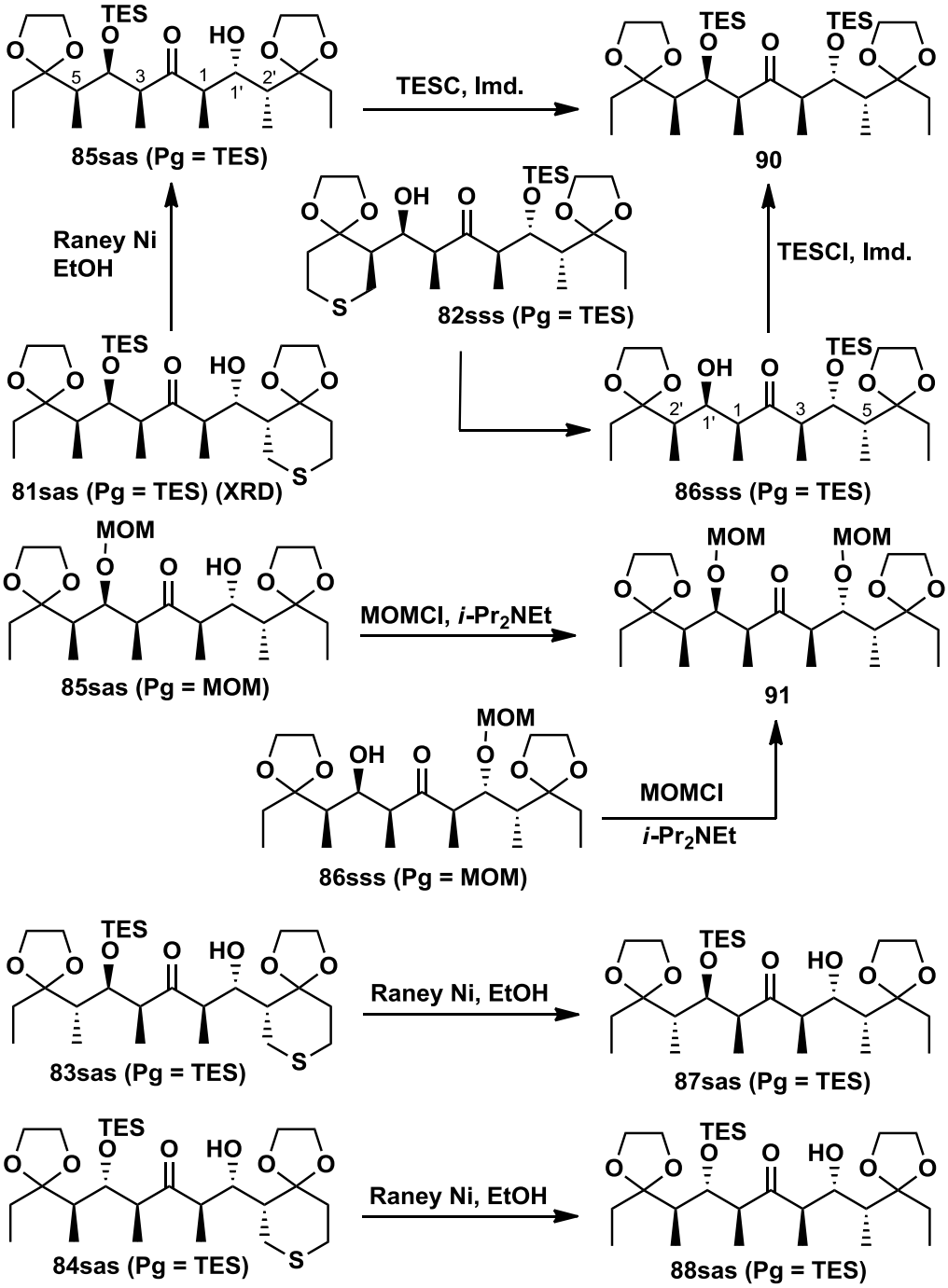
Aldol adduct **81sas** (Pg = TES) was found to be a crystalline solid. Therefore, its structure was confidently established by XRD analysis (see section Figure A.1 in Appendix). Because aldol adduct **85sas** (Pg = TES) was obtained by desulfurization of **81sas** (Pg = TES), its structure was established by this chemical correlation to **81sas** (Pg = TES) (Scheme 2.7). The structure of **86sss** (Pg = TES) was established by correlation to **85sas** (Pg = TES). Treatment of

* The aldol adducts prepared by the author are presented here. Aldol adducts prepared by others are omitted.

85sas (Pg = TES) with TESCl and imidazole (Imd.) provided **90**. The ^{1}H and ^{13}C NMR date for **90** were identical to those for the product of TES protection of **86sss** (Pg = TES) thereby establishing the structure of **86sss** (Pg = TES). The structure of **82sss** (Pg = TES) was established by desulfurization to give a product whose ^{1}H and ^{13}C NMR data were identical to those for **86sss** (Pg = TES). Reaction of **85sas** (Pg = MOM) with MOMCl and *i*-Pr_2NEt provided **91** whose ^{1}H and ^{13}C NMR data were identical to those for the product obtained from a similar reaction of **86sss** (Pg = MOM). Because the 3,4-4,5-relative configurations of the aldol adducts **85sas** (Pg = MOM) and **86sss** (Pg = MOM) are assumed to be identical to those of the corresponding starting ketones **62a** and **63a**, respectively, the above correlation established the 1,1′-1′,2′-relative configurations of both **85sas** (Pg = MOM) and **86sss** (Pg = MOM). The 1,3-relative configurations of **85sas** (Pg = MOM) and **86sss** (Pg = MOM) were assumed to be *syn* because these aldol adducts were obtained from the aldol couplings of (*E*)-enolborinates (of corresponding ketones with **29b**) that were found to be 1,3-*syn* selective in related aldol couplings with isobutyraldehyde (see section 2.2.2.).

Comparison of the ^{1}H and ^{13}C NMR data of the remaining **sas** aldol adducts (**83sas** (Pg = TES), **84sas** (Pg = TES), **87sas** (Pg = TES), and **88sas** (Pg = TES)) with those from **60** and **61** established the 1,1′- and 1′,2′-relative configurations of these adducts. Similar to the structure establishment of **85sas** (Pg = MOM) and **86sss** (Pg = MOM), the 1,3-relative configurations of **83sas** (Pg = TES), **84sas** (Pg = TES), **87sas** (Pg = TES), and **88sas** (Pg = TES) were assumed to be *syn*. These assignments were further supported by chemical correlations between the aldol adducts. For example, desulfurizations of **83sas** (Pg = TES) and **84sas** (Pg = TES) provided **87sas** (Pg = TES) and **88sas** (Pg = TES), respectively, establishing that their relative configurations are identical.

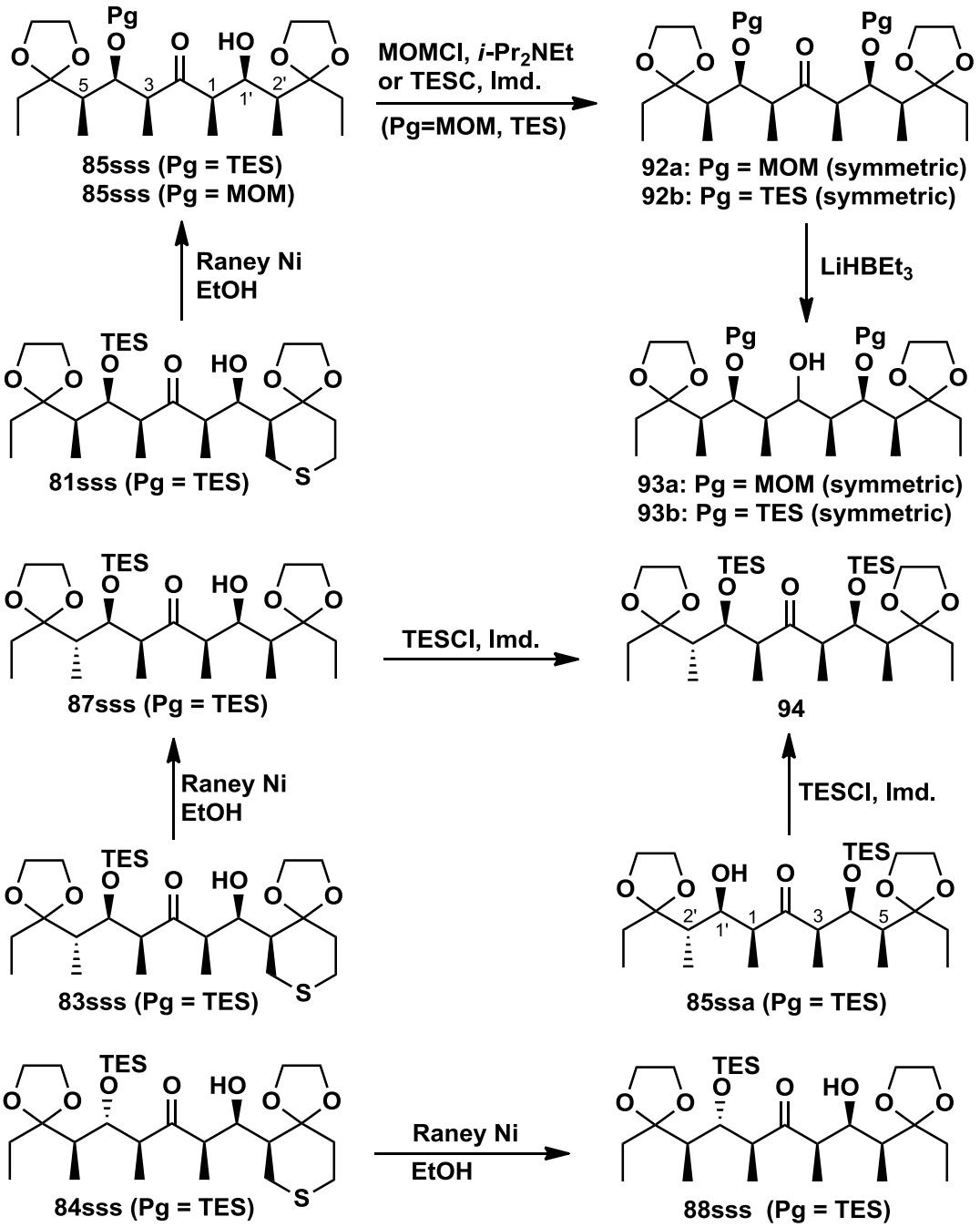
Scheme 2.7. Structure determination of **sas** aldol adducts.*



*Derivatizations of **82sss** (Pg = TES) and **86sss** (Pg = MOM) were performed by Kundu, D.

Having secured the structures of all **sas** aldol adducts, the next focus was to establish the structures of remaining **sss** and **ssa** aldol adducts. Toward that end, the structures of **85sss** (Pg = MOM, TES) (Scheme 2.8) were established first by taking advantage of the symmetry elements present in simple derivatives of these aldol adducts (e.g., when Pg = H). Inspection of the structures of **85sss** (Pg = TES) suggests that TES protection or deprotection can lead to a symmetric compound (e.g., **92b**). Similarly, MOM protection or deprotection of **85sss** (Pg = MOM) can also lead to a symmetric compound (e.g., **92a**). If **92a** and **92b** are symmetric, then the number of proton and carbon signals in their NMR spectra should be dramatically reduced (ca. half that of an unsymmetric diastereomer). Indeed, MOM protection of **85sss** (Pg = MOM) and TES protection of **85sss** (Pg = TES) provided **92a** and **92b**, respectively, each of which was shown to be symmetric by NMR. To determine whether **92a** and **92b** have a plane (σ (sigma)) or axis of symmetry (C_2), both were reduced with super hydride ($LiHBEt_3$). Reduction of ketones with a plane of symmetry will give symmetric alcohols whereas reduction of C_2 symmetric ketones will give asymmetric alcohols. Both reduced products **93a** and **93b** were shown to be symmetric by NMR establishing that they (and the precursor ketones **92a** and **92b**) have a plane of symmetry (σ). Thus, **85sss** (Pg = MOM) and **85sss** (Pg = TES) must have 1,3-*syn*-1,1′-*syn*-1′,2′-*syn* (sss) relative configurations. To establish the structure of **81sss** (Pg = TES), desulfurization was performed. The ^{1}H and ^{13}C NMR data of the resulting product were identical to those for **85sss** (Pg = TES), establishing the 1,3-*syn*-1,1′-*syn*-1′,2′-*syn* (sss) relative configurations for **81sss** (Pg = TES). The structures of **87sss** (Pg = TES) and **85ssa** (Pg =TES) were established by chemical correlations — treatment of both **87sss** (Pg = TES) and **85ssa** (Pg =TES) with TESCl and imidazole afforded compound **94**. Because the 3,4-4,5-relative configurations of both **87sss** (Pg = TES) and **85ssa** (Pg =TES) are identical to those of the precursor ketones **64b** and **62b**, respectively, the above correlation established the 1,1′-*syn*-1′,2′-*syn* (ss) relative configurations for **87sss** (Pg = TES) and 1,1′-*syn*-1′,2′-*anti* (sa) relative configurations for **85ssa** (Pg =TES). The 1,3-relative configurations of these aldol adducts were assumed to be *syn* because these aldol adducts were obtained from the reactions of (*Z*)-enol borinates that selectively gave 1,3-*syn* aldol adducts in reactions with isobutyraldehyde (see section 2.2.2.).

Scheme 2.8. Structure determination of **sss** and **ssa** aldol adduct.*



*Derivatizations of **83sss** (Pg = TES) and **84sss** (Pg = TES) were performed by Kundu, D.

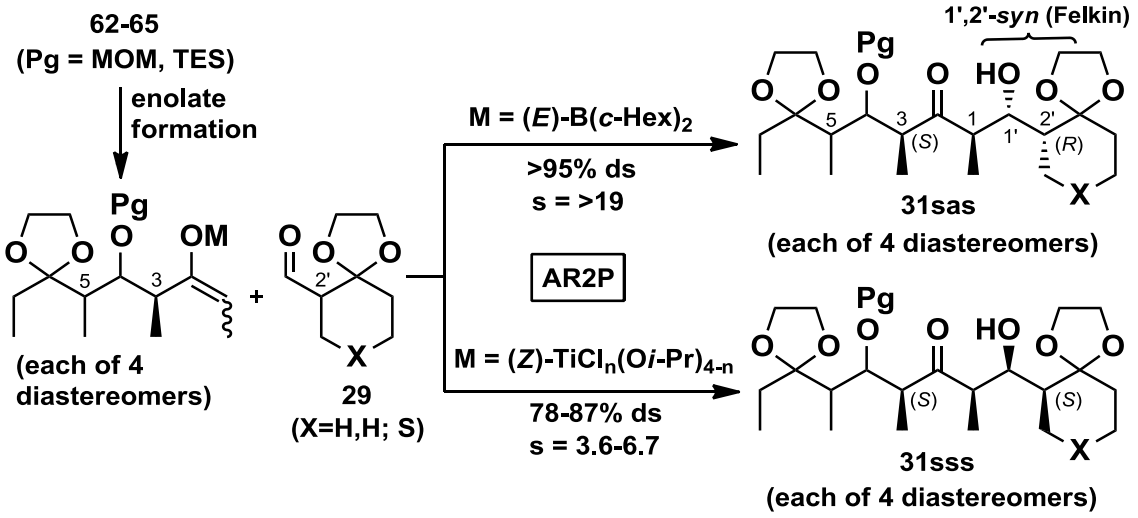
The structures of **83sss** (Pg = TES)**, 82sss** (Pg = TES), and **84sss** (Pg = TES) were established by desulfurization to give **87sss** (Pg = TES), **86sss** (Pg = TES), and **88sss** (Pg = TES), respectively (Scheme 2.8).

With the relative configurations established for all **sas** and **sss** diastereomers, the NMR data for each of these aldols were carefully analyzed and a NMR database was generated. Comparison of the NMR data of **ass** diastereomers with the above database allowed direct assignments of 1,1′-*syn* and 1′,2′-*anti* relative configurations of **ass** diastereomers. The 1,3-relative configurations of **ass** diastereomers could be either *syn* or *anti*. Because the **sss** diastereomers were assigned to have 1,3-*syn* relative configurations (Scheme 2.8), the **ass** diastereomers must have 1,3-*anti* relative configurations.

2.2.5. Summary

The additions of achiral enolate **59** (derived from 3-pentanone) to **29** were Felkin selective in the absence of chelation and provided 1′,2′-*syn* (Felkin) aldols as the major products. In contrast, the additions were non-Felkin selective in the presence of chelation and gave 1′,2′-*anti* (non-Felkin) aldols as the predominant products. In general, the aldol couplings of **29a** with **59** were more diastereoselective than similar aldol couplings with **29b**. The aldol couplings of (*E*)-enol borinates and Ti(IV) (*Z*)-enolates of **62-65** with isobutyraldehyde (**70**) afforded good to excellent diastereoselectivities. Therefore, the aldol couplings of **29** were performed with (*E*)-enol borinates and Ti(IV) (*Z*)-enolates of **62-65**. Due to the ease of access to Li (*Z*)-enolates, the aldol coupling of Li (*Z*)-enolates of **62-65** and **29a** were also investigated. Consistent with the predictions of the multiplicativity rule, the aldol couplings of (*E*)-enol dicyclohexylborinates of **62-65** with **29** proceeded with excellent MKEs and provided 1,3-*syn*-1,1′-*anti*-1′,2′-*syn* (**sas**) diastereomers as the exclusive products. In contrast, the aldol couplings of Ti(IV) (*Z*)-enolates of **62-65** with **29** proceeded with moderate MKEs and provided 1,3-*syn*-1,1′-*syn*-1′,2′-*syn* (**sss**) diastereomers as the major products. The aldol couplings of **29a** with (*E*)-enol borinates and Ti(IV) (*Z*)-enolates of non-racemic **62b-65b** (aldol with KR) provided the **sas** and **sss** aldol adducts in enantiomerically enriched form that were used in the isomerization study (section 2.3.4.7.).

Scheme 2.9. Aldol couplings (with KR) of acyclic ketones (AR2P).



2.3. Stereoselective synthesis of non-Felkin aldols

Isomerization of aldol adducts is a potential strategy to access diastereomers unobtainable via directed aldol couplings. Stereoselective directed aldol couplings are typically performed under kinetically controlled conditions (e.g., lower temperatures) resulting in irreversible formation of the products.[42, 47] Unfortunately, little attention has been given to the thermodynamic equilibration (i.e., reversibility) of aldols or their metal aldolates.[47] Problems associated with such equilibrations result from several undesired transformations (e.g., elimination, low product ratios after equilibration) that are possible under the equilibration conditions. Isomerization of aldol adducts can occur through two different pathways: i) keto-enol tautomerization (Figure 2.6) and ii) retroaldol-aldol reaction (Figure 2.7). Isomerization via keto-enol tautomerization is often mediated by weak bases such as hydroxides, alkoxides, or amines.[126] The base facilitates the formation of enol **96a** from aldol **95ss** (Figure 2.6). The stereochemical information at the α-stereocenter is lost in enol **96a**. Tautomerization of enol **96a** returns **95ss** or a new diastereomer, **95aa**. During the formation of **95aa**, the α-stereocenter gets inverted but the β-stereocenter remains unchanged. Similarly, tautomerization of **95ss** at the α′-stereocenter can lead to the formation of a new diastereomer, **95as** through the formation of enol **96b**. A few examples of such isomerizations have been reported in the literature. [123, 127-129] Typically mixtures of aldol adducts were obtained with low diastereomeric ratios. As a result, it has limited applications in polypropionate syntheses.[109, 128, 130-131]

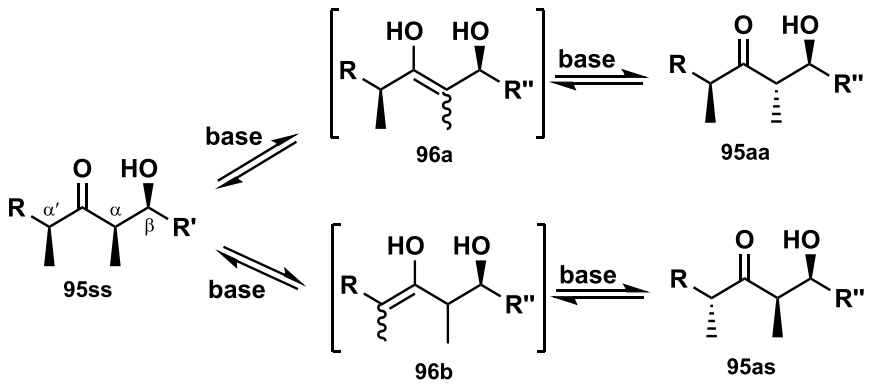


Figure 2.6. Isomerization via keto-enol tautomerization.

In retroaldol-aldol isomerization under base catalysis, the β-OH group of aldol **95ss** undergoes deprotonation to form the corresponding aldolate **96ss** (Figure 2.7). Aldolate **96ss** can then undergo a retroaldol reaction to generate enolate **19a** and aldehyde **5**. A subsequent aldol coupling between **19a** and **5** can lead to aldolates **96ss**, **96aa**, **96sa**, and **96as** where either one (α (**96aa**) or β (**96sa**)) or both (α and β in **96as**) of the stereocenters in the starting **96ss** are inverted. Protonation of these metal aldolates **96** forms the corresponding aldol diastereomers **95**. The number of possible diastereomers that can be formed in a retroaldol-aldol isomerization is identical to that of a directed aldol coupling reaction. The retroaldol-aldol isomerization under acid catalysis follows similar reaction pathway and proceeds through the formation of enol **19** and aldehyde **5**.

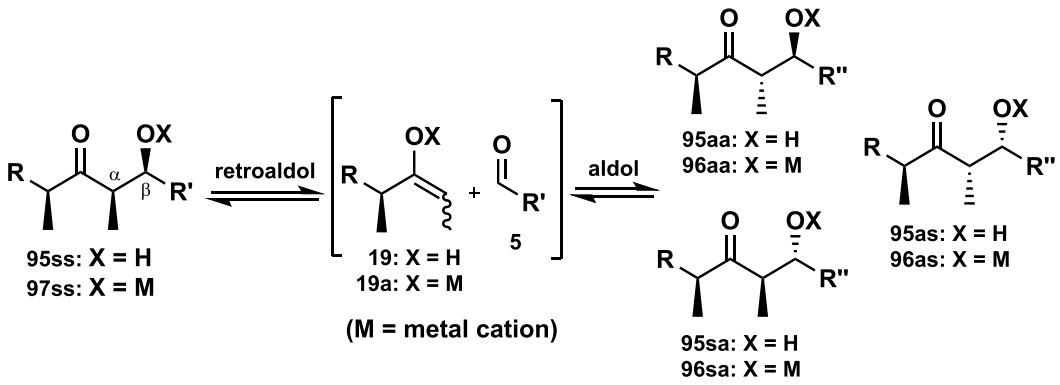


Figure 2.7. Isomerization via retroaldol-aldol mechanism.

β-Hydroxy carbonyl compounds such as **95** (X = H, Figure 2.7) are prone to elimination under acidic and basic conditions. Thus, finding suitable conditions for retroaldol-aldol isomerization is often extremely challenging. Contrary to the difficulties associated with the

isomerization of aldols, metal-aldolates such as Ba(II),[130] Zn(II),[42, 107] Mg(II)[132-133] and Ti(IV)[125] aldolates have successfully been exploited in isomerizations.

2.3.1. Objectives

The Ward group has made significant progress in the area of polypropionate syntheses and successfully applied these approaches (i.e., TR2P) in total syntheses of polypropionate natural products.[81] Extensive investigation has focussed on accessing all of the eight possible aldols diastereomers that result from an aldol coupling of **29** with enolate of **97** (Figure 2.8) without significant modification of the reactants. The thiopyran route to polypropionates (TR2P)[84] and the acyclic route to polypropionates (AR2P) provided selective access to four of the eight possible diastereomers. The diastereoface selectivities of addition of **29** to enolates of **97** were found to be 1,3-*anti* selective in the TR2P (**E**: 1,3-*anti*) and provided selective access to 1,3-*anti* aldol adducts **98aas** and **98ass**. In contrast, the additions were 1,3-*syn* selective in the AR2P (**E**: 1,3-*syn*) and provided selective access to 1,3-*syn* aldol adducts **98sas** and **98sss**. Depending on the conditions, both 1,1′-*syn* and 1,1′-*anti* selective reactions were achieved in both the routes (**R**: 1,1′-*syn*/*anti*) providing 1,1′-*syn* (**98ass** and **98sss**) and 1,1′-*anti* (**98aas** and **98sas**) aldol adducts. Four of the eight possible diastereomers (**98aas**, **98ass**, **98sas**, and **98sss**) obtained via TR2P and AR2P have 1′,2′-*syn* relative configurations suggesting the diastereoface selectivities of additions of enolates of **97** to **29** are 1′,2′-*syn* (Felkin) selective in both the routes (**A**: 1′,2′-*syn*). Switching the diastereoface selectivities of addition of enolates of **97** to **29** (**A**) to 1′,2′-*anti* (non-Felkin) selective would provide access to the remaining four diastereomers. Although the remaining 1′,2′-*anti* (non-Felkin) diastereomers have been detected in various aldol reactions in the Ward group,[134] they have rarely been isolated and only as minor products. There are no methods reported in the literature to-date to selectively access 1′,2′-*anti* (non-Felkin) aldols **98ssa**, **98asa**, **98saa**, and **98aaa** from the aldol couplings of **97** and **29**, without significant modifications of the coupling fragments. Hence, the main objective for the current project was to develop a method(s) that would provide access to most (if not all) of the remaining 1′,2′-*anti* (non-Felkin) aldols illustrated in Figure 2.8.

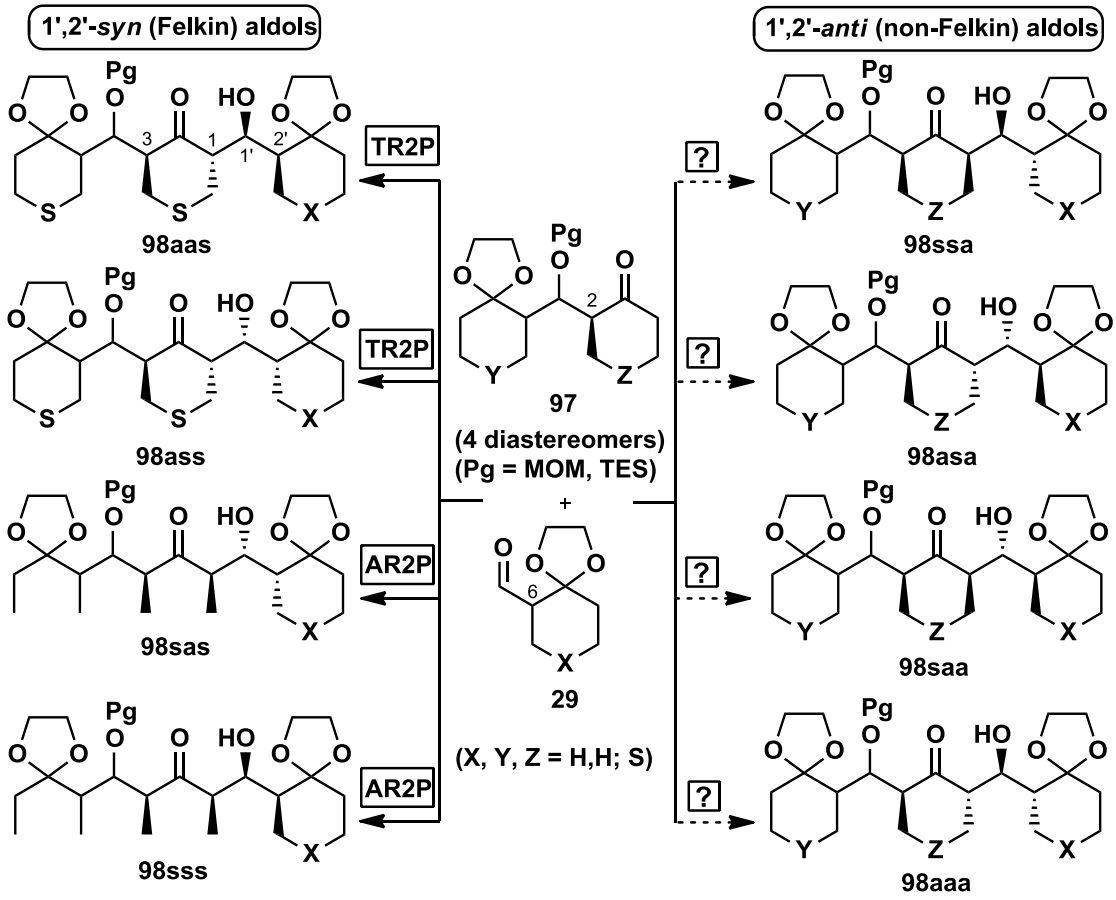
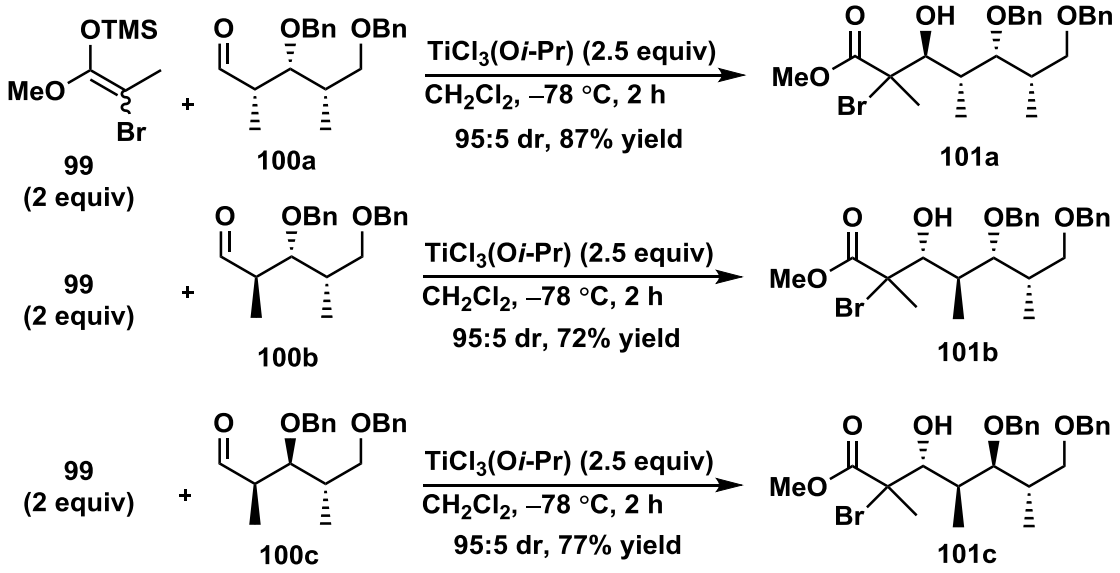


Figure 2.8. Aldol coupling of chiral ketones with chiral aldehydes.

2.3.2. Mukaiyama aldol couplings using $TiCl_3(O\textit{i}\text{-Pr})$

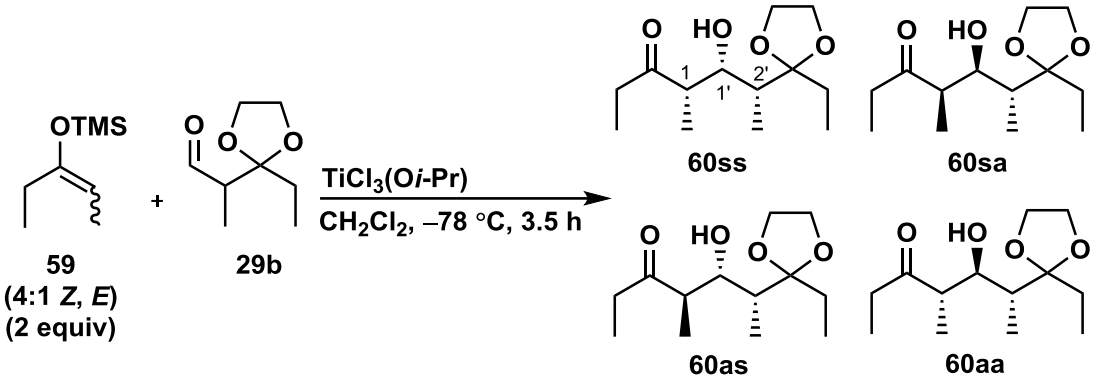
Guindon *et al*. developed a strategy to access 1′,2′-*anti* (non-Felkin) aldols of acyclic aldehydes (**100**) with excellent diastereoselectivities (95:5) via Mukaiyama aldol couplings of **99** and **100** mediated with $TiCl_3(O\textit{i}\text{-Pr})$ (Scheme 2.10).[135] Therefore, $TiCl_3(O\textit{i}\text{-Pr})$ promoted Mukaiyama aldol coupling of **5** with **29b** (Table 2.16) was investigated at −78 °C (kinetic control) in an effort to access the corresponding 1′,2′-*anti* (non-Felkin) aldols, **11sa** and **11aa**. Following the procedure reported by Urpí *et al*.,[136-137] $TiCl_3(O\textit{i}\text{-Pr})$ was prepared and used immediately.

Scheme 2.10. Guindon's work on $TiCl_3(O\textit{i}\text{-Pr})$ mediated Mukaiyama aldol couplings of **99** and **100**.



Guindon *et al*. reported that the use of 2.5 equiv of $TiCl_3(O\textit{i}\text{-Pr})$ affords results superior to those obtained with 1.1 equiv.[135] Consequently, 1.1 and 2.5 equiv of $TiCl_3(O\textit{i}\text{-Pr})$ were used for the current investigation (Table 2.16). Consistent with the observation of Guindon *et al*.,[135] excellent non-Felkin selectivity was obtained using 2.5 equiv of $TiCl_3(O\textit{i}\text{-Pr})$ whereas lower diastereoselectivity was obtained using 1.1 equiv of $TiCl_3(O\textit{i}\text{-Pr})$ (compare entries 1 and 2). It should be noted that the reaction shown in Table 2.16 (entry 2) is the best route to-date to access the 1,1′-*syn*-1′,2′-*anti* (**sa**) diastereomer (**60sa**) with excellent diastereoselectivity.

Table 2.16. Mukaiyama aldol coupling of **59** with **29b** using $TiCl_3(O$*i*-Pr).

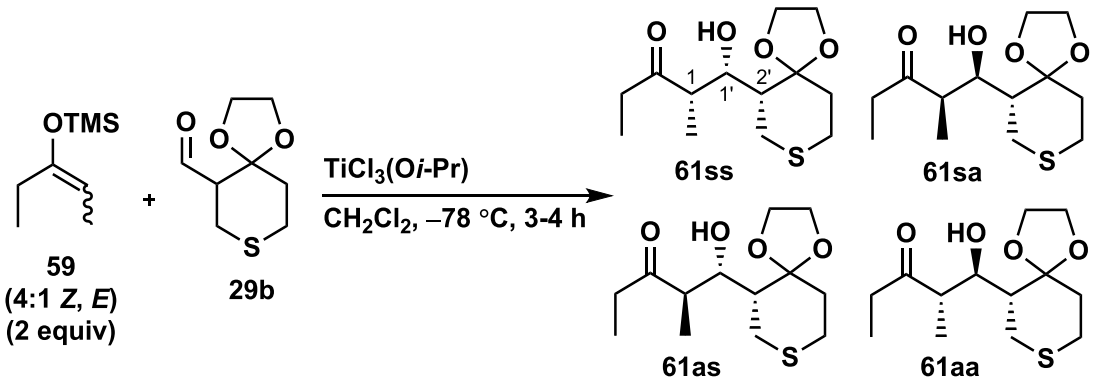


entry	equiv[a]	convn[b,c](%)	sa:aa:ss:as[b]	non-Felkin:Felkin[d]	yield[e]
1	1.1	>95%	75:13:6:6	7.2:1	ND[f]
2	2.5	>95%	83:9:4:4	11:1	88

[a]Equivalents of $TiCl_3(O$*i*-Pr) with respect to 1 equiv of aldehyde used. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Estimated from the ratio of aldol products to aldehyde present in the crude reaction mixture. [d]Refers to the ratio Σ(**sa**+**aa**) to Σ(**ss**+**as**). [e]Isolated yield of the indicated mixture of diastereomers. [f]Not determined.

To explore the substrate scope of the above reaction, aldehyde **29a** was also screened under conditions identical to those used for **29b** (Table 2.17). A mixture of all four possible aldols were detected by ^{1}H NMR of the crude reaction mixture when either 1.1 or 2.5 equiv of $TiCl_3(O$*i*-Pr) was used (entries 1 and 2). Surprisingly, 1.1 equiv of $TiCl_3(O$*i*-Pr) afforded better diastereoselectivity than that obtained with 2.5 equiv. Thus, 1.1 equiv of $TiCl_3(O$*i*-Pr) was used in all subsequent reactions.

Table 2.17. Mukaiyama aldol coupling of **59** with **29a** using $TiCl_3(O\textit{i}\text{-Pr})$.



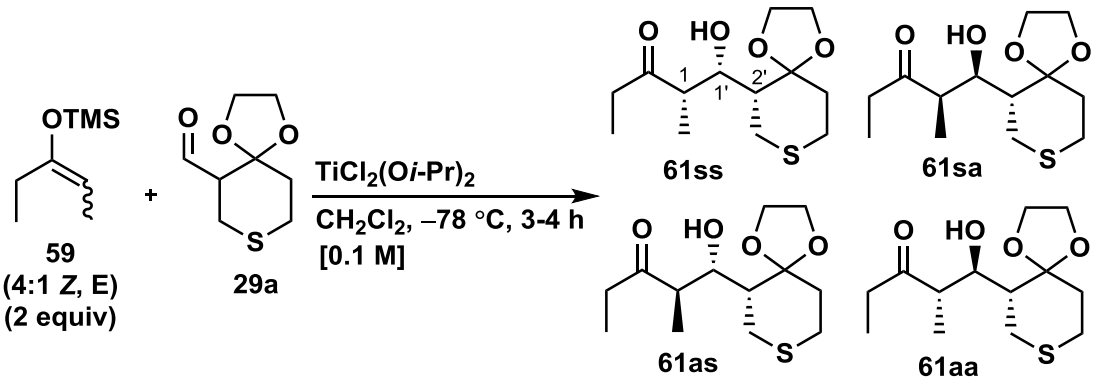
entry	conc[a] (M)	equiv[b]	convn[c,d] (%)	selectivity[c] (sa:aa:ss:as)	non-Felkin:Felkin[d]
1	0.1	1.1	92	42:28:19:11	2.3:1
2	0.1	2.5	95	29:8:21:42	1:1.7
3[e]	0.1	1.1	>95	48:25:16:11	2.5:1
4[e]	0.1	2.5	>95	28:10:28:34	1:1.6
5	0.2	1.1	91	41:29:18:12	2.3:1
6	0.05	1.1	>95(91)[f]	63:23:9:5	6.3:1
7	0.02	1.1	89	53:26:14:7	3.7:1

[a]Concentration of the total reaction mixture. [b]Equivalent of $TiCl_3(O\textit{i}\text{-Pr})$ with respect to 1 equiv of aldehyde used. [c]Determined by ^{1}H NMR of the crude reaction mixture. [d]Estimated by ^{1}H NMR from the ratio of aldol adducts to aldehyde present in the crude reaction mixture. [d]Refers to the ratio Σ(**sa**+**aa**) to Σ(**ss**+**as**). [e]Solid $TiCl_3(O\textit{i}\text{-Pr})$ was dissolved in CH_2Cl_2 and used as a stock solution. [f]Isolated yield (in percent) of the indicated mixture of diastereomers.

It was speculated that low diastereoselectivities resulted from the presence of multiple titanium species. While the above method of preparing $TiCl_3(O\textit{i}\text{-Pr})$ provides $TiCl_3(O\textit{i}\text{-Pr})$ as the major species in solution, other species with general formula $TiCl_{4-n}(O\textit{i}\text{-Pr})_n$ (n = 0-4) may also be present, perhaps causing low diastereoselectivity. To avoid the presence of multiple titanium species and potentially improve non-Felkin selectivity, pure $TiCl_3(O\textit{i}\text{-Pr})$ was prepared following the reported procedure.[138] The product was isolated as a pale yellow colored solid and dissolved in dichloromethane to make a stock solution. Use of this stock solution afforded results (entries 3

and 4) comparable to those obtained with *in situ* generated of $TiCl_3(O\textit{i}\text{-Pr})$.[136-137] Consequently, the later method was used to prepare $TiCl_3(O\textit{i}\text{-Pr})$ in all subsequent experiments. A significant change in the diastereoselectivity was observed when the concentration of the reaction was varied (entries 5-7) and 0.05 M was found to be optimal (entry 6).

Table 2.18. Mukaiyama aldol coupling of **59** with **29a** using $TiCl_2(O\textit{i}\text{-Pr})_2$.



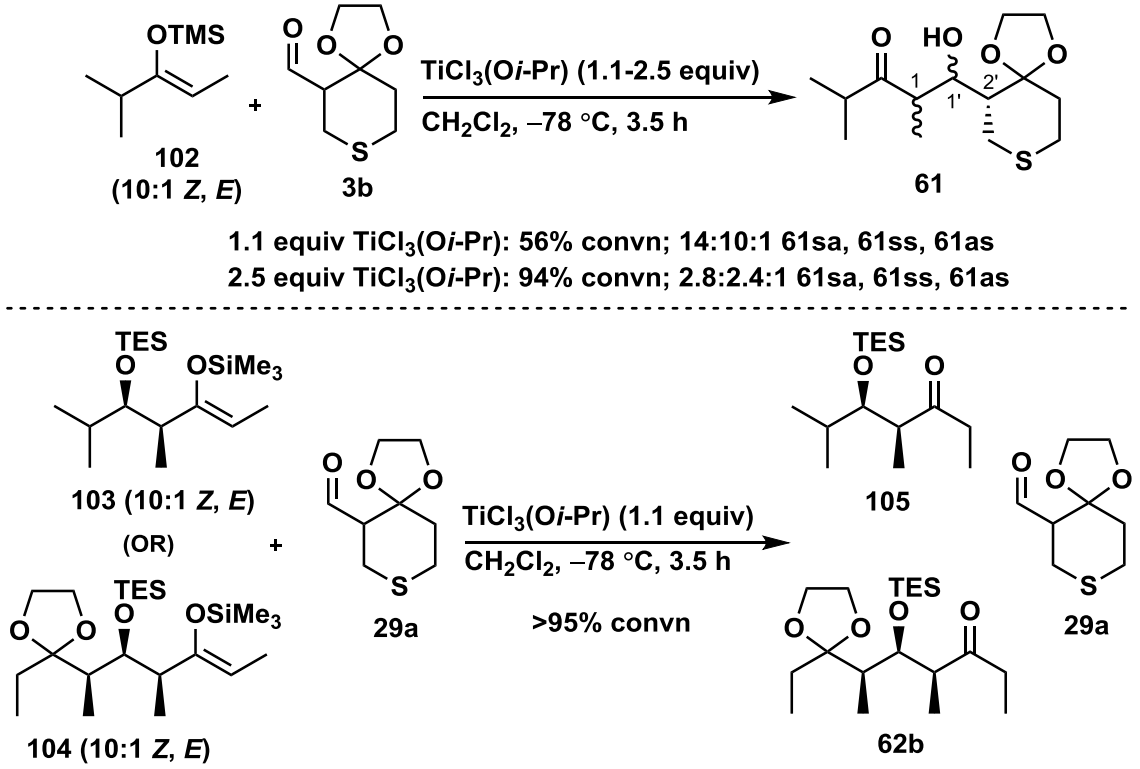
entry	equiv[a]	convn[b,c](%)	sa:aa:ss:as[b,c]	non-Felkin:Felkin[d]
1	1.1	<10	NA	NA
2	2.5	>95	36:8:24:32	1:1.3

[a]Equivalents of $TiCl_3(O\textit{i}\text{-Pr})$ with respect to 1 equiv of aldehyde used. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Estimated by ^{1}H NMR from the ratio of aldol adducts to aldehyde present in the crude reaction mixture. [d]Refers to the ratio Σ(**sa**+**aa**) to Σ(**ss**+**as**).

In an effort to improve the diastereoselectivity, $TiCl_2(O\textit{i}\text{-Pr})_2$ was tested for the Mukaiyama aldol coupling of **59** with **29a** under similar conditions as described in Table 2.17. The $TiCl_2(O\textit{i}\text{-Pr})_2$ was prepared following the procedure reported by Urpí *et al.*[136-137] Aldol coupling with 1.1 equiv of $TiCl_2(O\textit{i}\text{-Pr})_2$ did not produce any aldol adduct (entry 1, Table 2.18). In contrast, complete consumption of **29a** was observed with 2.5 equiv of $TiCl_2(O\textit{i}\text{-Pr})_2$. However, the amount of desired 1′,2′-*anti* (non-Felkin) aldols was significantly lower than that obtained using $TiCl_3(O\textit{i}\text{-Pr})$. Hence, the latter was used for further investigation. The aldol coupling of **102**[53] with **29a** under the reaction conditions identical to those used for **59** provided a ~1:1 mixture of 1′,2′-*anti* (non-Felkin) and 1′,2′-*syn* (Felkin) aldols. Interestingly, similar diastereoselectivities were observed when either 1.1 or 2.5 equiv of $TiCl_3(O\textit{i}\text{-Pr})$ were used. Aldol couplings of **103** and

104 with **29a** (Scheme 2.11) under the conditions similar to those used for **59** (*cf*. Table 2.17) did not afford any aldol adduct. Instead, complete decompositions of the enol ethers to the corresponding ketones were observed.

Scheme 2.11. Mukaiyama aldol couplings of **102-104*** with **29a** using $TiCl_3(O$*i*-Pr).



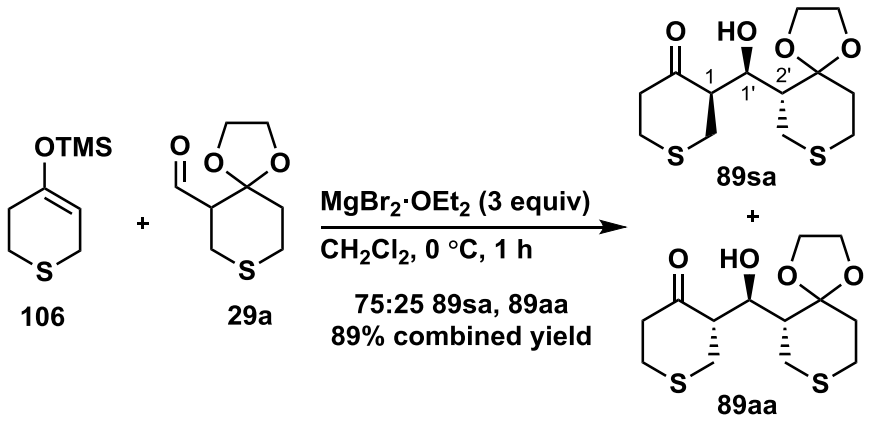
2.3.3. Mukaiyama aldol couplings using $MgBr_2 \cdot OEt_2$

In search for an alternate Lewis acid to promote the Mukaiyama aldol coupling of chiral enol ethers (e.g., **103**, **104**) with **29a**, $MgBr_2 \cdot OEt_2$ was selected for further investigation. Ward *et al*. have reported the Mukaiyama aldol coupling of **29a** with **106** using $MgBr_2 \cdot OEt_2$ as the Lewis acid (Scheme 2.12).[108] The aldol coupling provided a 75:25 mixture of **89sa** and **89aa** in 89% combined isolated yield. It is worth pointing out that both the products have 1′,2′-*anti* relative configurations, suggesting highly selective non-Felkin addition to **29a** under the above conditions.

* Enol ethers **103** and **104** were only characterized by ^{1}H NMR spectroscopy.

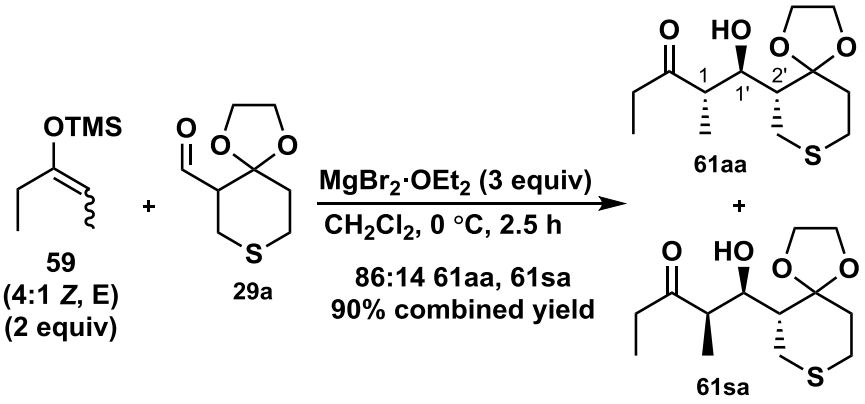
When the same reaction was performed with **(+)-29a**, aldols **(+)-89sa** and **(+)-89aa** were obtained in comparable yield and diastereomeric ratio as with racemic **29a**.[84]

Scheme 2.12. Ward's work on Mukaiyama aldol coupling of **29a** with **106** using $MgBr_2 \cdot OEt_2$.



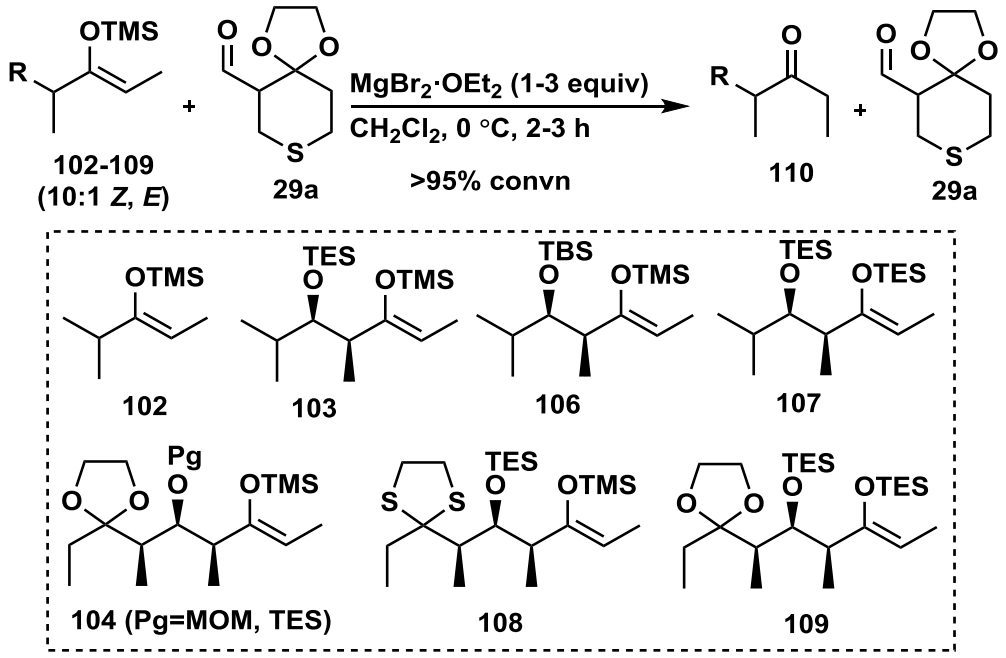
Because of the structural similarity between **59** and **106**, an attempt to perform the aldol coupling of **59** with **29a** in the presence of $MgBr_2 \cdot OEt_2$ was made (Scheme 2.13). The ^1H NMR spectrum of the crude product indicated the presence of a 86:14 mixture of **61aa** and **61sa**, respectively. Fractionation of the crude product provided 90% combined isolated yield of the products. To-date, this reaction provides the best route to access the challenging 1,1′-*anti*-1′,2′-*anti* (**aa**) aldol diastereomer **61aa**. This reaction has been successfully used to access one of the key coupling fragments (i.e., ketone) in the total synthesis of dolabriferol C.[139] Once again, both **61sa** and **61aa** have 1′,2′-*anti* relative configurations suggesting highly selective non-Felkin addition to **29a** under the above reaction conditions.

Scheme 2.13. Mukaiyama aldol coupling of **59** with **29a** using $MgBr_2 \cdot OEt_2$.



The aldol couplings of chiral enol ethers (**102-109**) with **29a** were also explored under the reaction conditions similar to those used for **59** (Scheme 2.14). In contrast to the results obtained with **59**, complete decompositions of the enol ethers (**102-109**) to their corresponding ketones (**110**) were observed.

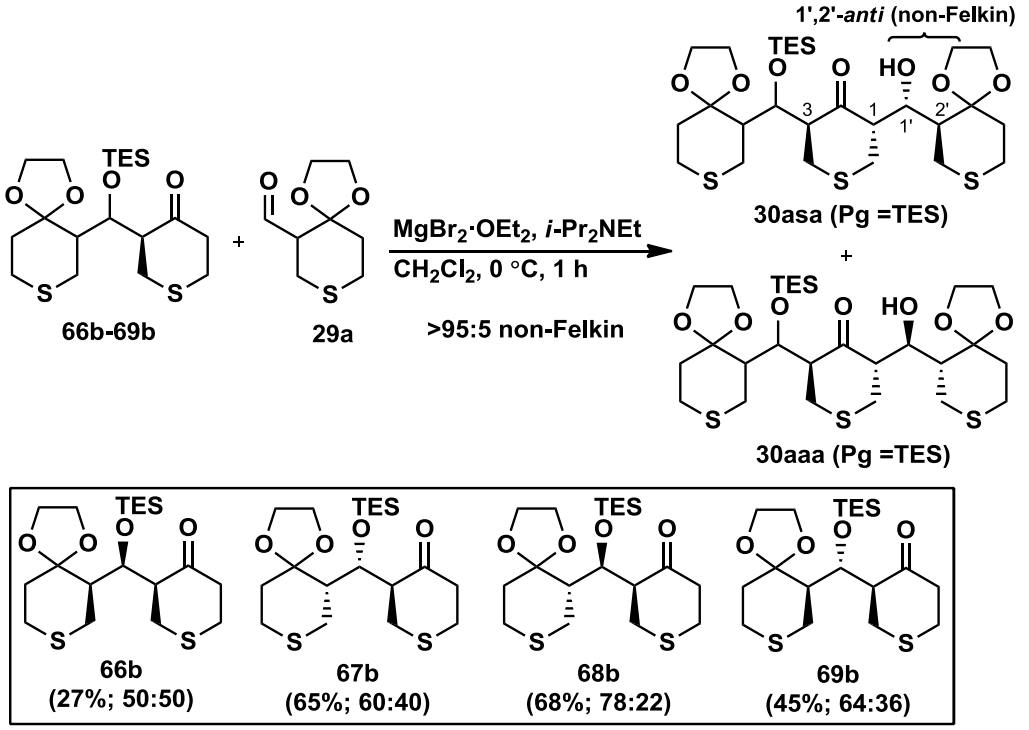
Scheme 2.14. Mukaiyama aldol couplings of **102-109*** with **29a** using $MgBr_2 \cdot OEt_2$.



* Enol ethers **103**, **104**, and **106-109** were only characterized by ^1H NMR spectroscopy.

The $TiCl_3(O\textit{i}\text{-Pr})$ promoted aldol coupling of **59** with **29b** provided access to 1,1′-*syn*-1′,2′-*anti* (**sa**) diastereomer **60sa** (Table 2.16) whereas similar aldol coupling with **29a** using $MgBr_2 \cdot OEt_2$ provided access to 1,1′-*anti*-1′,2′-*anti* (**aa)** diastereomer **61aa** (Scheme 2.13). Both $TiCl_3(O\textit{i}\text{-Pr})$ (Scheme 2.11) and $MgBr_2 \cdot OEt_2$ (Scheme 2.14) promoted Mukaiyama aldol couplings of chiral enol ethers (**102-109**) with **29a** failed to produce the desired 1′,2′-*anti* (non-Felkin) aldols in any reasonable amount. In search for an alternate method to access the 1′,2′-*anti* (non-Felkin) aldols of chiral ketones or chiral enol ethers, the next focus was to investigate the aldol couplings of Mg(II) enolates.

Scheme 2.15. Ward's approach toward non-Felkin aldols.*



The aldol couplings of Mg(II) enolates of **66b-69b**, generated using $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt, with **29a** had been previously investigated in the Ward group (Scheme 2.15).[134] Mixtures

* Section 2.3. mostly deals with aldols adducts of TES protected ketones. Therefore, the labellings of these aldol adducts are simplified by omitting the protecting group (Pg). For example, aldol **30asa** (Pg = TES) will be simply referred to as **30asa**.

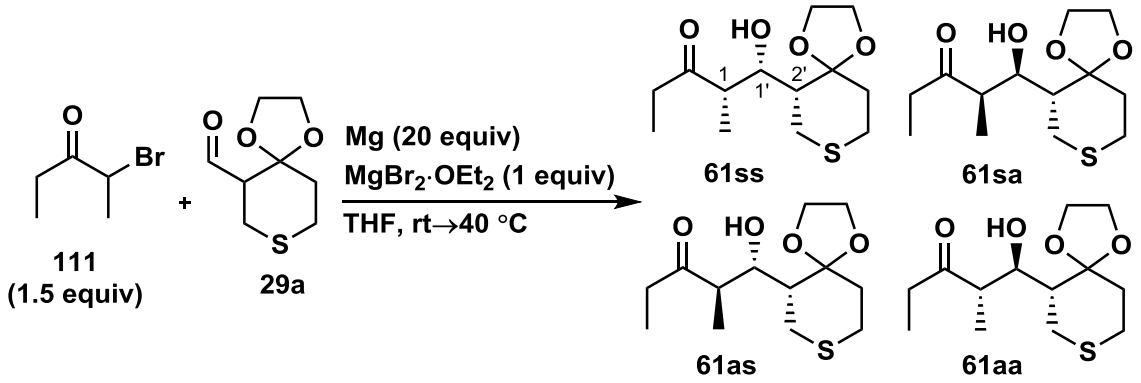
of **30asa** and **30aaa** were obtained in ratios ranging from 50:50 to 78:22. It is important to note that both **30asa** and **30aaa** have 1′,2′-*anti* relative configurations. The isolated yields of the products were low (28%) to moderate (68%) and often variable and scale dependent. To avoid the reproducibility issue, an alternate strategy was adopted to generate the Mg(II) enolates. It has been reported in the literature that Mg(II) enolates can be generated by reacting acyclic α-bromoketones with metallic magnesium.[43, 140-141] Consequently, acyclic bromoketones were used to investigate the aldol couplings of various Mg(II) enolates with **29a** which are discussed below.

2.3.4. Isomerization of Mg(II) aldolates

2.3.4.1. Use of α-bromoketones to generate Mg(II) aldolates

Following the published procedure, 2-bromo-3-pentanone **111**[142] was prepared in excellent yield. Based on the literature precedents,[143] it was anticipated that the reaction of **111** with freshly activated Mg metal in THF would result in formation of the corresponding Mg(II) enolate which could be trapped with **29a** (Table 2.19). The Lewis acid $MgBr_2 \cdot OEt_2$ was used as an additive in an effort induce chelation controlled non-Felkin (1′,2′-*anti*) addition to **29a**. No reaction was observed at room temperature even after 24 hours (entry 1). When the reaction mixture was heated to 40 °C for 0.5 h, complete consumption of **29a** (>95% conversion) was observed and a mixture of aldol adducts was obtained (entry 2). The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of 69% of 1′,2′-*anti* (non-Felkin) aldols, **61sa** and **61aa**. The presence of 31% of 1,1′-*anti-1′,2′-syn* diastereomer **61as** was also detected but the 1,1′-*syn*-1′,2′-*syn* diastereomer **61ss** was not observed. The presence of a large amount of 1′,2′-*anti* (non-Felkin) aldols prompted further investigation. Surprisingly, when the reaction was continued at 40 °C for longer time, the initially formed **61as** and then **61aa** disappeared over time, resulting in a single diastereomer **61sa** after 24 h (entry 5). Slow decomposition of the Mg(II) aldolates with an increase in the amount of **29a** was observed when the reaction time was further increased to 48 h at 40 °C (entry 6). Repetition of the same reaction for 24 h at 40 °C provided **61sa** in 83% yield.

Table 2.19. Reaction of Mg(II) enolate of **111** with **29a**.



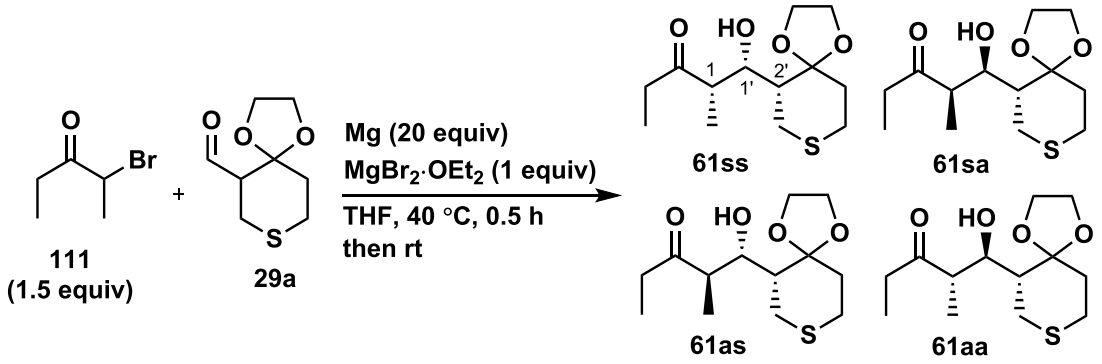
entry	temp	time (h)	convn[a](%)	(sa:aa:as)[a,b]	non-Felkin:Felkin[c]
1	rt	24 h	0	NA	NA
2	40 ˚C	0.5	>95	49:20:31	69:31
3	40 ˚C	2	>95	72:16:12	69:31
4	40 ˚C	4	>95	78:13:9	91:9
5	40 ˚C	24	91	>95:5 **61sa**	>95:5
6	40 ˚C	48	90	>95:5 **61sa**	>95:5

[a]Estimated by ^{1}H NMR from the ratio of aldol adducts to aldehyde present in the crude reaction mixture. [b]The **61ss** diastereomer was not detected by ^{1}H NMR. [c]Ratio of the sum of 1′,2′-*anti* (non-Felkin) and the sum of 1′,2′-*syn* (Felkin) aldol adducts.

To determine the effect of $MgBr_2 \cdot OEt_2$ on the product distribution, parallel experiments were conducted with and without $MgBr_2 \cdot OEt_2$. No significant effect was observed between the two reactions in the early stages, but the presence of added $MgBr_2 \cdot OEt_2$ was found to be crucial to achieve high yields and diastereoselectivities. Moreover, it was found that the results were more reproducible if the reaction was performed in a sealed Schlenk tube. Consequently, all subsequent reactions with $MgBr_2 \cdot OEt_2$ were performed in a Schlenk tube under argon atmosphere. To determine the effect of temperature, the isomerization was performed at room temperature. As mentioned in Table 2.19, heating was crucial for the Mg insertion step to generate the Mg(II) enolate of **111**. Consequently, the reaction mixture was heated to 40℃ for 0.5 h to generate the Mg(II) enolate and then stirred at room temperature over several hours (Table 2.20). The progress

of the reaction was monitored by ^{1}H NMR by quenching aliquots at different time intervals. The results in Table 2.20 suggest that isomerization occurs at a slower rate at room temperature and the reaction did not reach equilibrium even after 56 h; the expected equilibrium ratio is >95:5 according to the results shown in Table 2.19. Therefore, 40℃ was chosen as the optimal temperature for further investigation.

Table 2.20. Isomerization of Mg(II) aldolates of **111** at room temperature.

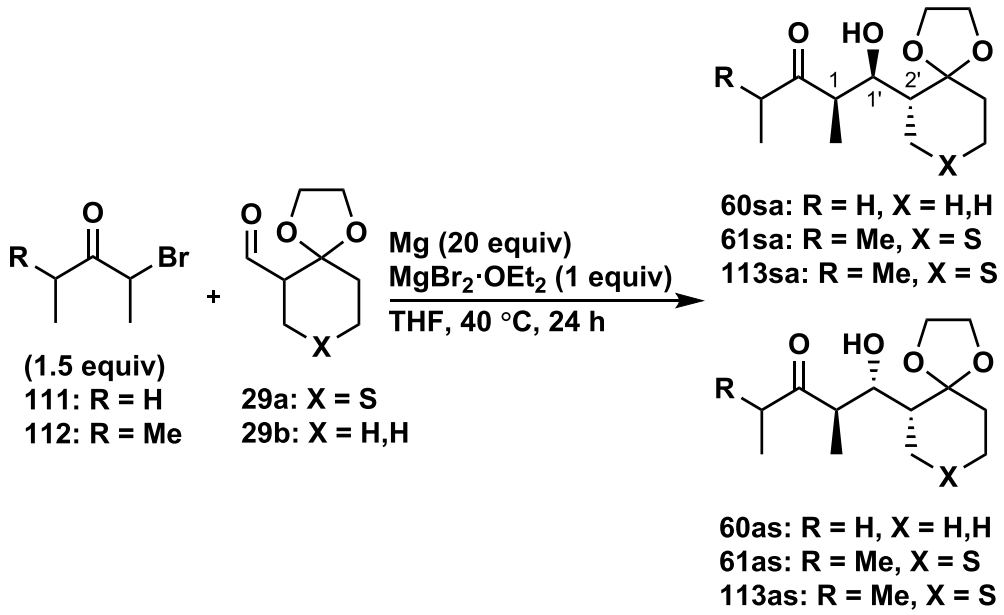


entry	time (h)	convn[a](%)	(sa:aa:as)[a,b]	non-Felkin:Felkin[c]
1	8	>95	62:17:21	79:21
2	24	>95	73:14:13	87:13
3	56	>95	83:9:8	92:8

[a]Estimated by ^{1}H NMR from the ratio of aldol adducts to aldehyde present in the crude reaction mixture. [b]The **ss** diastereomer was not detected by ^{1}H NMR. [c]Ratio of the sum of 1′,2′-*anti* (non-Felkin) and the sum of 1′,2′-*syn* (Felkin) aldol adducts.

Bromoketones **111**, **112**[142] and aldehydes **29a**, **29b** were screened under the reaction conditions described in Table 2.19 and the results are summarized in Table 2.21. In the case of cyclic aldehyde (**29a**), one of four possible diastereomers was obtained in aldol couplings with both **111** and **112** (entries 1 and 2). Similar aldol coupling of **111** with acyclic aldehyde (**29b**) provided a 70:30 mixture of two of the four possible diastereomers (entry 3, Table 2.21). Consequently, **29a** was selected for further investigation.

Table 2.21. Screening of substrates for isomerization.



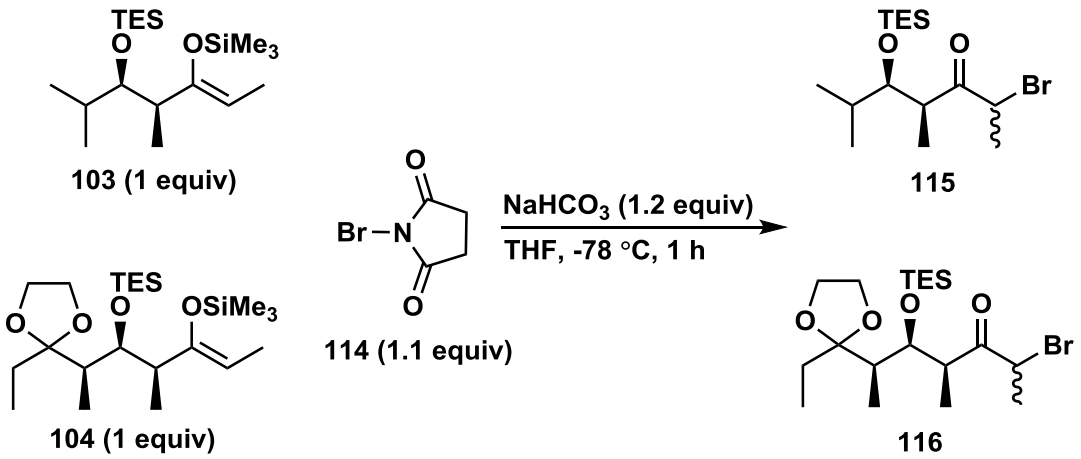
entry	bromoketone	aldehyde	equilibrium ratio[a,b]	non-Felkin:Felkin[c]	isolated yield[d] (%)
1	**111**	**29a**	>95:5 **61sa**	>95:5	83
2	**112**	**29a**	>95:5 **113sa**	>95:5	81
3	**111**	**29b**	70:30 **60sa**, **60as**	70:30	78[e]

[a]Estimated by ^{1}H NMR from the ratio of aldol adducts to aldehyde present in the crude reaction mixture. [b]Equilibrium was confirmed by running the reaction for longer time — no significant change in the ratio was observed by ^{1}H NMR. [c]Ratio of the sum of 1′,2′-*anti* (non-Felkin) and the sum of 1′,2′-*syn* (Felkin) aldol adducts. [d]Isolated yield of **sa**. [e]Combined isolated yield of **sa** and **as**.

To explore the substrate scope of the above isomerization study, chiral bromoketones were used. The aldol coupling of Mg(II) enolate of a chiral bromoketone with **29a** can produce up to eight possible diastereomers. Now, the question was - would it still be possible to obtain non-Felkin (1′,2′-*anti*) aldols with high selectivity after isomerization? Towards this goal, bromoketones **115** and **116** (Table 2.22) were selected for investigation. Unfortunately, all efforts to synthesize these bromoketones by direct bromination of the Li enolates of the corresponding ketones (**105** and **62b**) using molecular bromine (Br_2) proved futile.[144] An alternate method using TMS-enol ethers and N-bromosuccinimide (**114**) proved more successful.[145-146] Thus, the reaction

of chiral TMS-enol ethers **103** and **104** with **114** in the presence of sodium bicarbonate ($NaHCO_3$) in THF cleanly provided bromoketones **115** (55:45 dr) in 80% yield and **116** (67:33 dr) in 77% yield, respectively as a mixture of diastereomers which was used for the next reaction.

Table 2.22. Preparation of chiral bromoketones **115-116***.



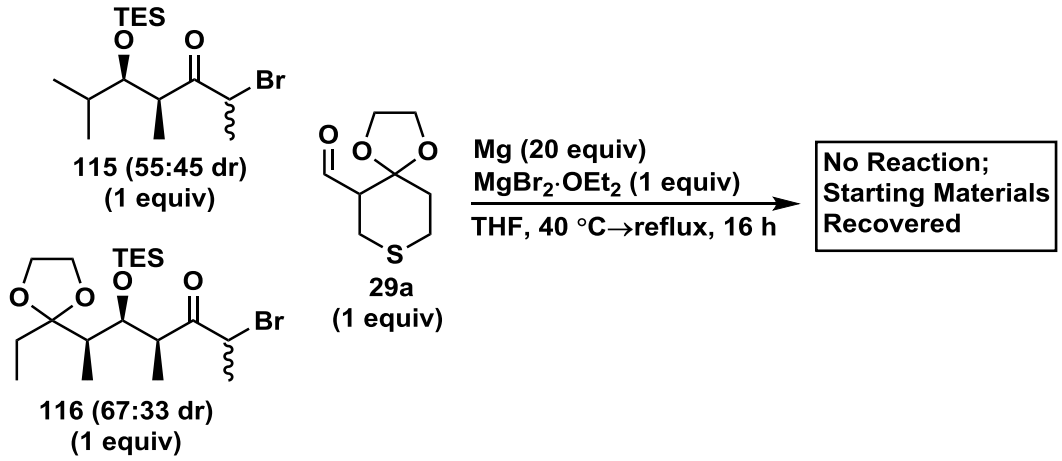
entry	enol ether[a]	convn[b,c](%)	selectivity[d] (dr)	isolated yield[e] (%)
1	**103**	>95	55:45	80
2	**104**	>95	67:33	77

[a]A >10:1 mixture of (*Z*)- and (*E*)-enol ether was used as starting material. [b]Estimated by ^{1}H NMR from the ratio of bromoketones to TMS-enol ether present in the crude reaction mixture. [c]Presence of ~ 6% of the corresponding ketones (**105** and **62b**) were also detected. [d]Determined by ^{1}H NMR of the crude reaction mixture. [e]Combined isolated yield of the mixture of diastereomers.

Attempted reactions of **115** and **116** with **29a** under the conditions described in Scheme 2.16 did not produce any detectable amount of aldol adducts. Increasing the reaction time or temperature had no beneficial effect. Starting bromoketones **115** and **116** as well as the unreacted aldehyde **29a** were recovered. Recovery of bromoketones **115** and **116** confirms the corresponding Mg(II) enolates were not generated under the reaction conditions.

* Compounds **115** and **116** were only characterized by ^{1}H NMR spectroscopy.

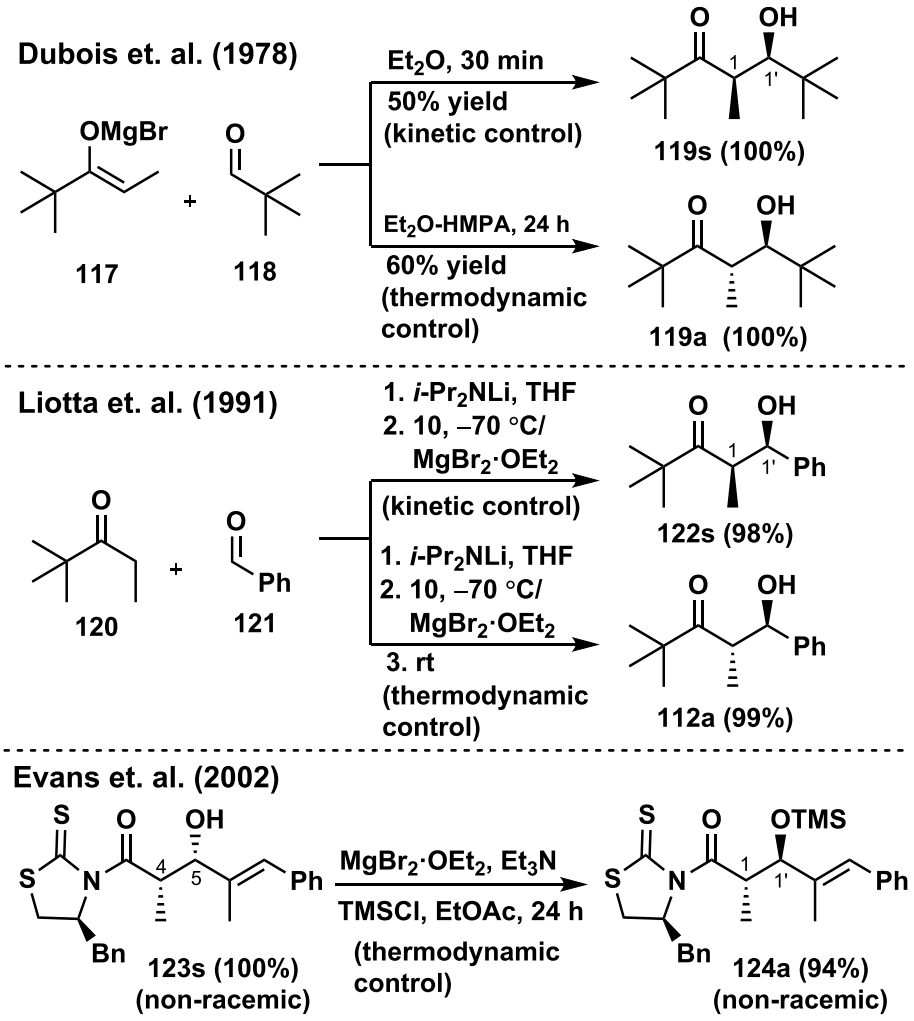
Scheme 2.16. Attempted reactions of **115** and **116** with **29a**.



2.3.4.2. Use of ketones to generate to Mg(II) aldolates

Scattered examples of isomerization of Mg(II) aldolates are reported in the literature. For instance, in 1978, Dubois and Fellmann reported that the reaction of **117** with pivalaldehyde (**118**) forms 1,1′-*syn* aldol adduct **119s** exclusively under kinetically controlled conditions (Scheme 2.17).[147] Conversely, the 1,1′-*anti* aldol adduct **119a** was the exclusive product when the reaction time was extended in presence of additive HMPA (hexamethylphosphoramide).[148] It was postulated that kinetically formed Mg(II) aldolates of **119s** underwent equilibration and formed thermodynamically more stable Mg(II) aldolate of **119a**. In 1972, the same authors also reported the aldol reaction between **117** and benzaldehyde (**121**) at 20 °C (not shown in Scheme 2.17).[132] The product distribution was found to be dependent on the reaction time, suggesting equilibration of the *in situ* formed Mg(II) aldolates. The 1,1′-*syn* aldol **119s** was formed exclusively (>95:5) under kinetic control (shorter reaction time) and the 1,1′-*anti* aldol **119a** was formed exclusively (>95:5) under thermodynamic control (longer reaction time).

Scheme 2.17. Literature examples of isomerization of Mg(II) aldolates.

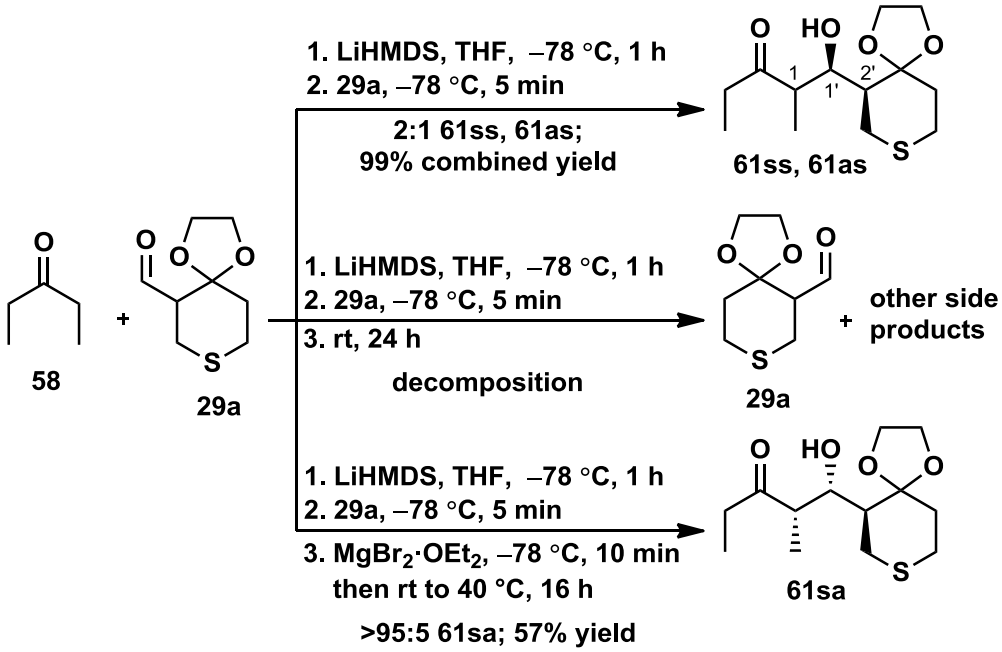


Liotta *et al*. studied the isomerization of various Mg(II) aldolates of achiral ketones and aldehydes.[133] The Mg(II) aldolates were generated from Li aldolates (or enolates) by treatment with $MgBr_2 \cdot OEt_2$ in THF (Scheme 2.17). Alternatively, the Mg(II) enolates were directly generated from a ketone by the treatment with chloromagnesium diisopropylamide (*i*-Pr_2NMgCl). Under kinetic control, both the methods provided the 1,1′-*syn* aldol **122s** as the major diastereomer. When the reaction mixture was warmed to room temperature, the 1,1′-*anti* aldol **122a** became the principal diastereomer. Another relevant example of isomerization of BrMg-aldolates was reported by Evans *et al*.[149] In this study, each of the four possible enantiomerically enriched diastereomers of **123s** were treated with $MgBr_2 \cdot OEt_2$ and Et_3N in ethyl acetate for 24 h in the presence of TMSCl as a trapping reagent. In all cases, the TMS protected 1,1′-*anti* aldol **124a** was formed as the

predominant diastereomer (Scheme 2.17). Formation of **124a** with the opposite absolute configuration at C-5 stereocenter, suggests thermodynamic equilibration of the corresponding Mg(II) aldolates via a retroaldol-aldol mechanism.

The examples reported by Liotta *et al*.[133] suggest that ketones (instead of bromoketones) can be used directly as starting materials in isomerization of Mg(II) aldolates. The initial goal was to replicate the results obtained previously with bromoketone **111** (*cf*. entry 1, Table 2.21) using ketone **58** as the starting material. Following the established procedure in the Ward group,[150] the aldol reaction of **58** with **29a** was performed at −78 °C followed by addition of solid $MgBr_2 \cdot OEt_2$. The mixture was initially warmed to room temperature and then heated to 40 °C for 16 h (Scheme 2.18).

Scheme 2.18. Aldol couplings of **58** with **29a** followed by isomerization.

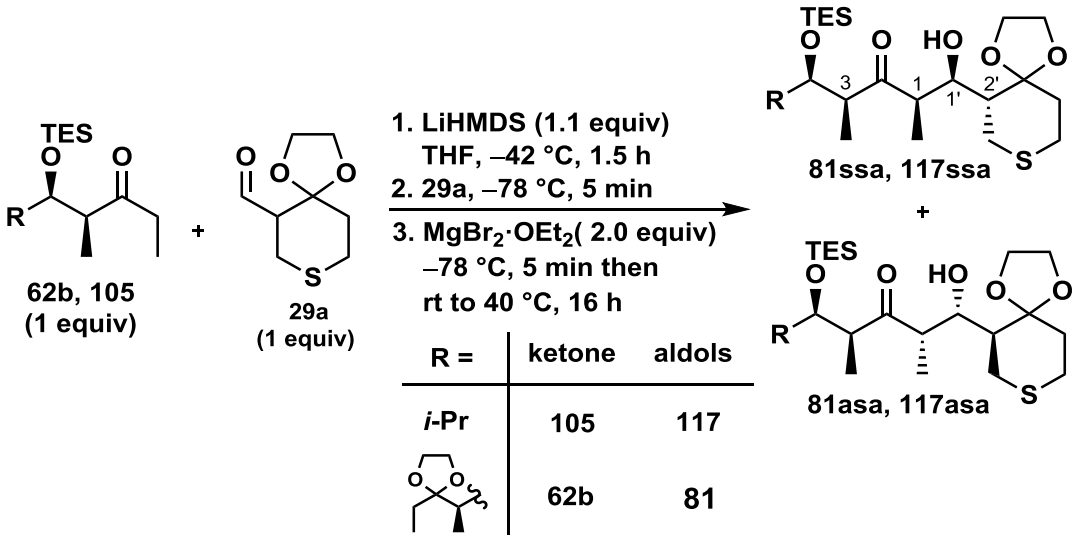


A single aldol adduct **61sa** was detected by ^{1}H NMR of the crude reaction mixture and isolated in 57% yield (Scheme 2.18). Therefore, it was possible to reproduce the diastereoselectivity (>95:5) observed in the reaction with **111**. The aldol coupling of **29a** with the Li enolate of **58** at −78 °C without the use of $MgBr_2 \cdot OEt_2$ provided a 2:1 mixture of **61ss** and **61as** in 99% combined isolated yield. Warming the reaction mixture to room temperature after the addition of **29a** at −78 °C provided **61aa** as the major product after 2 h. When the stirring was continued at room temperature for 24 h, no trace of aldol adduct was detected; only **29a** and

unidentified side products were present. Therefore, it can be concluded that the observed selectivity is not the result of isomerization of Li aldolates but from the isomerization of Mg(II) aldolates.

Because initial efforts to obtain 1′,2′-*anti* (non-Felkin) aldols of chiral ketones **62b** and **105** were unsuccessful, the next plan was to apply the reaction conditions described in Scheme 2.18 to these chiral ketones. Formation of Li enolates of chiral ketones such as **105**[115] and **62b**[124] has been reported in the literature. The reactions of the Li enolates of **105** and **62b** with **29a** (Table 2.23) were conducted under reaction conditions similar to those used for **58** (*cf*. Scheme 2.18).

Table 2.23. Isomerization of Mg(II) aldolates of **62b** and **105**.



entry	substrate	aldehyde present[a]	ketone present[a]	ssa:asa[a]	isolated yield[b] (%)
1	**105**	5%	22%	57:43	40
2	**62b**	5%	<5%	52:48	56

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Combined yield of **ssa** and **asa**.

For both the ketones, the ^{1}H NMR spectra of the crude reaction mixtures showed the presence of only two of the eight possible diastereomers (Table 2.23). All products have 1,1′-*syn*-1′,2′-*anti* (sa) relative configurations similar to **61sa**. Aldols **81ssa** and **117ssa** have 1,3-*syn*-1,1′-*syn*-1′,2′-*anti* (ssa) and **81asa** and **117asa** have 1,3-*anti*-1,1′-*syn*-1′,2′-*anti* (asa) relative

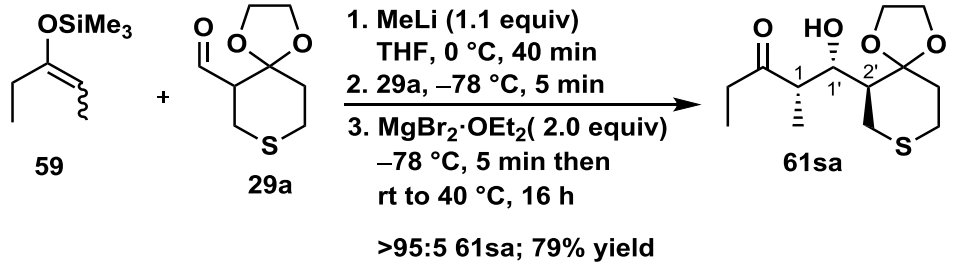
configurations (see section 2.3.5.). The combined isolated yields of the products were low (≤56%) for both reactions.

The yield of aldol adducts decreased with increased reaction time. Moreover, the amount of aldehyde (**29a**) detected in the reaction mixtures by ^{1}H NMR was less than the ketones (**62b** and **105**). One possible explanation for these observations is that **29a** is consumed by some other side reaction during isomerization. Deprotonations of the ketones with LiHMDS produce HMDS. It is possible that HMDS reacts with **29a** (formed *in situ* from the retroaldol of Mg(II) aldolates) in presence of $MgBr_2 \cdot OEt_2$; causing depletion of **29a** over time. To test this hypothesis, HMDS and *i*-Pr_2NH were added to the benchmark reaction shown in Table 2.21 (entry 1). After 24 h at 40 °C, <10% of the aldol adducts were detected by ^{1}H NMR whereas the reaction without any base yielded >80% of the desired aldol diastereomer (**61sa**). These control experiments suggest that LiHMDS or LDA cannot be used for the current isomerization study. Hence, it was necessary to perform the isomerization experiments in the absence of such bases.

2.3.4.3. Amine-free Li enolates to generate Mg(II) aldolates

Adapting the published procedure, amine-free Li enolate was generated from its TMS-enol ether **59** (Scheme 2.19).[108, 151] The aldol coupling of **29a** with Li enolate of **59** followed by isomerization was performed under the reaction conditions described in Scheme 2.18. A single aldol adduct **61sa** was isolated in 79% yield. The results in Scheme 2.19 were comparable in terms of diastereoselectivity (>95:5) and percent yield with those obtained with bromoketone **111** (entry 1, Table 2.21).

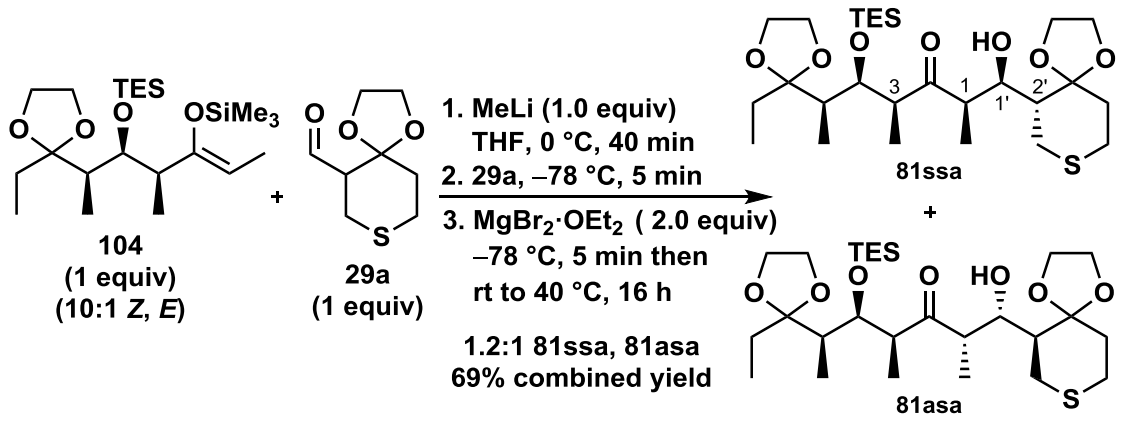
Scheme 2.19. Isomerization of Mg(II) aldolate of **59** under amine-free conditions.



Having the amine-free isomerization conditions in hand, the next goal was to perform the isomerization of Mg(II) aldolates of chiral ketones under these conditions. Following a similar

procedure as that used for **59**, the aldol coupling of **29a** with Li enolate of **104** (prepared by transmetallation with MeLi)[108] was performed followed by isomerization (Scheme 2.20). Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed the presence of two aldol diastereomers **81ssa** and **81asa** in a 55:45 ratio. This is consistent with the ratio reported in entry 2 (Table 2.23). The yield of the products could not be improved beyond 69% due to incomplete transmetallation from Si→Li; as evident from the presence of unreacted enol ether **104** in the crude reaction mixture.

Scheme 2.20. Isomerization of the Mg(II) aldolate of **104** under amine-free conditions.



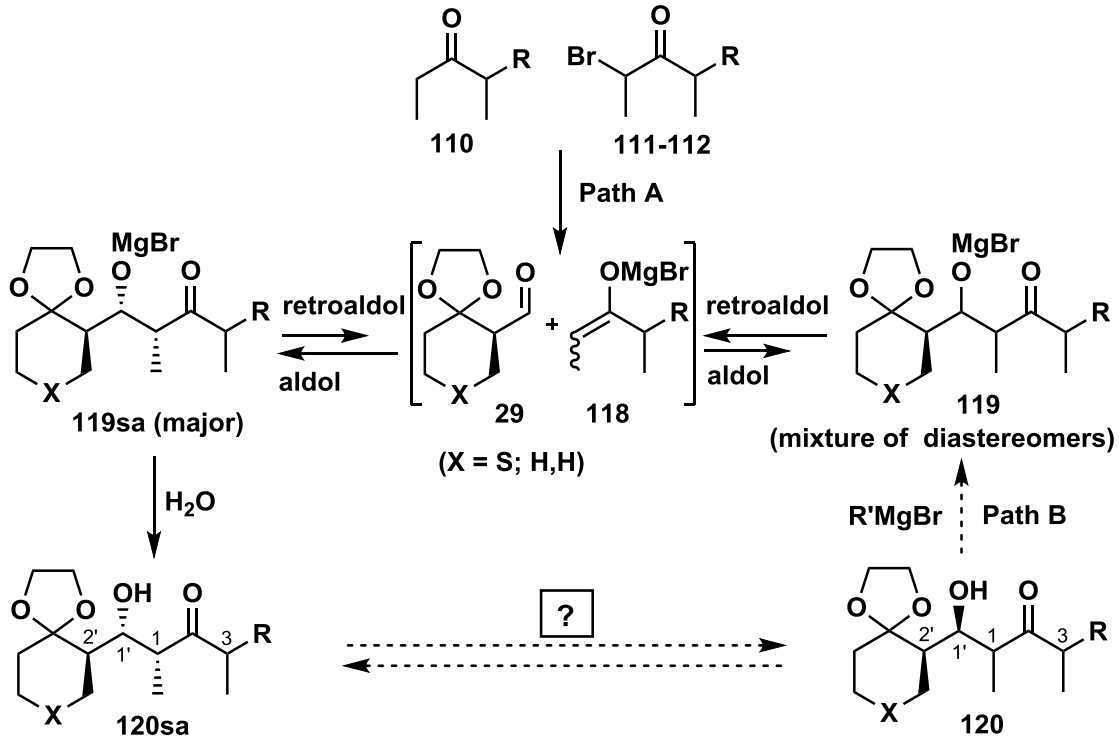
The results of retroaldol-aldol isomerization were identical irrespective of whether the $MgBr_2 \cdot OEt_2$ was added before or after the aldol reaction, consistent with the observations of Liotta *et al*.[133] Despite the limitations mentioned above, the reactions illustrated in Schemes 2.18-2.20 and Table 2.23 suggest that the 1′,2′-*anti* (non-Felkin) aldol adducts can be obtained from a ketone or its enol ether, avoiding the use of bromoketones.

2.3.4.4. Use of aldol adducts to generate of Mg(II) aldolates

As described above, different methods have been successfully developed to generate and isomerize Mg(II) aldolates of **29a**. A single non-Felkin (1′,2′-*anti*) aldol was obtained in isomerization of Mg(II) aldolates of achiral ketones and a ~1:1 mixture of two non-Felkin (1′,2′-*anti*) aldols was obtained in isomerization of Mg(II) aldolates of chiral ketones. To access enantiomerically enriched 1′,2′-*anti* (non-Felkin) aldols, a revised strategy was used. Based on

literature precedents[132-133, 147, 152] and the initial results of the isomerization study described above, a retroaldol-aldol mechanism is proposed for the isomerization of Mg(II) aldolates.

Scheme 2.21. Proposed pathways toward retroaldol-aldol isomerization of Mg(II) aldolates.

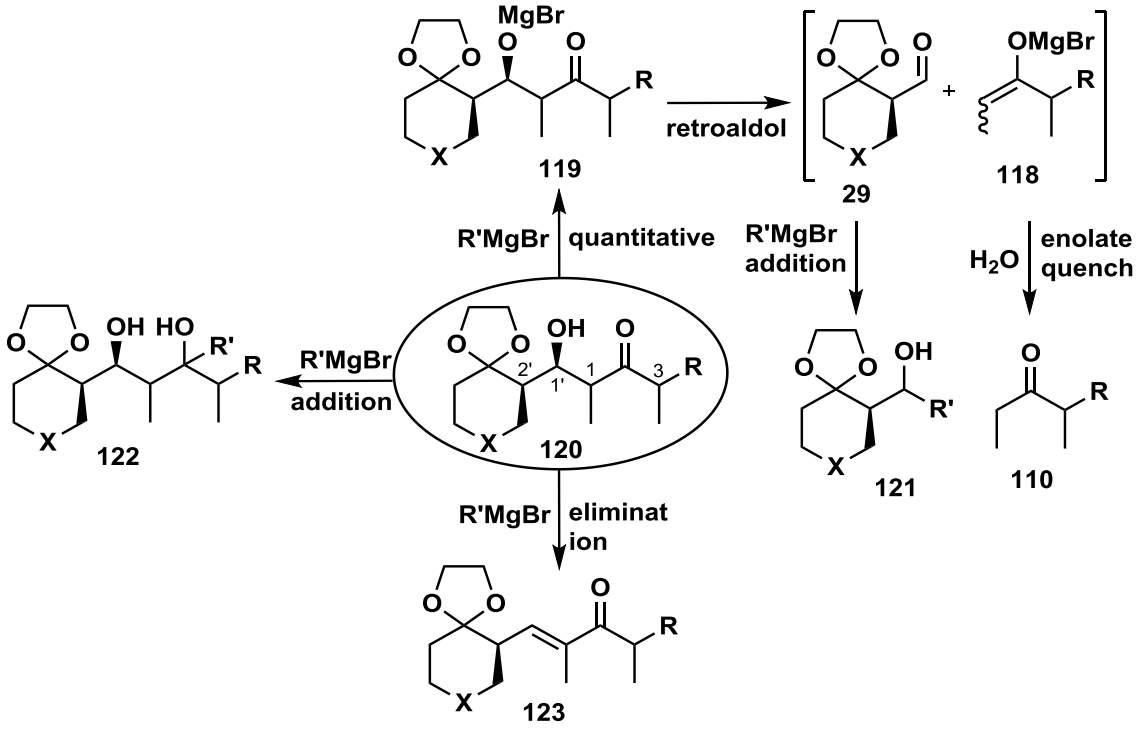


It was speculated that ketones (**110**) or bromoketones (**111-112**) initially form a mixture of Mg(II) (*Z*)-and (*E*)-enolates (**118**) (Path A, Scheme 2.21). The mixture of enolates reacts with **29a** to form a diastereomeric mixture of Mg(II) aldolates **119**. Aldolates **119** are not stable under the reaction conditions and undergo equilibration via a retroaldol-aldol mechanism to yield the thermodynamically most stable Mg(II) aldolate **119sa**. Workup of the reaction then provides the corresponding aldol **120sa** as the final product.

A similar pathway can be envisioned where an aldol adduct (**120**) may be used as the starting material (Path B, Scheme 2.21). A major advantage in using **120** as the starting material would be its simple preparation both in racemic and enantioenriched forms. The Ward group has successfully developed TR2P and AR2P to selectively access different 1′,2′-*syn* (Felkin) aldols in both racemic and enantioenriched form that can be used as the starting materials for the isomerization study. All attempts to quantitatively generate the Mg(II) aldolates from their

corresponding aldol adducts using $MgBr_2 \cdot OEt_2$ and tertiary amine bases (e.g., Et_3N, *i*-Pr_2NEt) in THF at 40℃ were unfruitful. A large amount of the corresponding aldehyde was detected by ^1H NMR of the crude reaction mixture and <20% of the 1′,2′-*anti* aldols were present. It was hypothesized that the by-products (i.e., ammonium salts) formed after deprotonation using tertiary amines are serving as a proton source, quenching the *in situ* formed Mg(II) enolates, resulting in a large amount of aldehyde. Because the equilibrium concentration of aldolates will be low under these conditions, any equilibration (if occurring) will be of aldol adducts instead of the corresponding metal aldolates. Consequently, the presence of by-products which cause unwanted side reactions during isomerization must be avoided. An exploration of deprotonating agents which would neither form any interfering side products nor leave any by-products in the reaction medium suggested Grignard reagents as reliable bases. Short chain alkyl Grignard reagents (R′MgBr) were used as they do not leave any by-products in the reaction medium because the by-product alkane (R′H) is typically a gas.

Scheme 2.22. Possible side reactions in deprotonation of aldols using Grignard reagent.



There are several challenges to overcome in using an alkyl Grignard (R′MgBr) to deprotonate aldol **120** (Scheme 2.22). First, aldol **120** needed to be converted to the corresponding Mg(II) aldolate **119** *quantitatively* because it was believed that the Mg(II) aldolates undergo

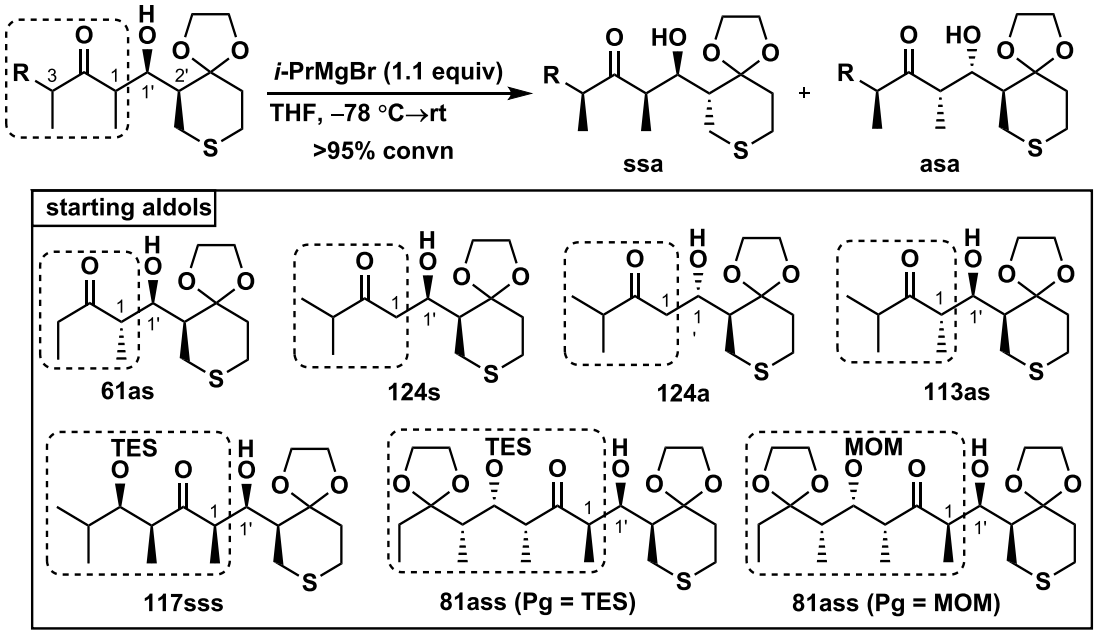
isomerization not the corresponding aldols. Indeed, use of substoichiometric amounts (<1 equiv with respect to the aldol used) of Grignard reagent resulted in incomplete equilibration; providing a mixture of aldol diastereomers as the final product. Second, due to their inherent basicity and nucleophilicity Grignard reagents can cause side reactions such as addition to carbonyls or elimination, resulting in undesired **122** and **123**, respectively. Finally, if the retroaldol-aldol process is interrupted by some other side reactions such as quenching of enolate (**118**) in the presence of moisture or Grignard addition to the *in situ* formed aldehyde (**29**), then the anticipated isomerization will be hampered. Attempting to address these challenges, the isomerization reaction was explored using *i*-PrMgBr as the base.

The initial aim was to use racemic (instead of enantioenriched) aldol adducts as the starting materials and reproduce the results obtained via the previous methods (see section 2.4.4.). The initial study attempted to reproduce the results obtained from the reaction of 3-pentanone (**58**) or its analogues (**59**, **111**) with **29a** (see Table 2.21 and Schemes 2.18-2.20). Toward this goal, aldol **61as** was treated with *i*-PrMgBr in THF at −78 °C followed by heating at 40℃. After 16 h, a single isomer (**61sa**) was isolated in 60% yield. It was found that yield of the product decreases with increasing reaction time at 40 °C. To improve the yield, the subsequent reactions were performed at room temperature. Under optimized conditions, **61sa** was isolated in 70% yield (entry 1, Table 2.24). No significant side products were observed under these conditions.

2.3.4.5. Effects of the ketone fragment of the starting aldol on isomerization

To determine the effect of a methyl group at the C-1 position in Table 2.24, aldol **124s** was prepared and subjected to the optimized conditions (entry 2, Table 2.24). Aldol **124s** was found to be highly susceptible to elimination and provided a 62:38 mixture of the two possible aldol adducts. Comparing entries 1 and 2 in Table 2.24, it can be concluded that the presence of a methyl group at the C-1 position is crucial to avoid elimination and for effective isomerization. Consequently, different ethyl ketones were used for further investigation. To explore the effect of substitution at the C-3 position in Table 2.24, aldol **113as** was subjected to the same conditions as **61as**. A single aldol adduct (**113sa**) was obtained in 84% yield (entry 3). Once again, no significant side products were detected under these reaction conditions.

Table 2.24. Retroaldol-aldol isomerization of Mg(II) aldolates of aldol adducts with varying ketone strcutures.



entry	starting aldol	time	equilibrium ratio[a,b] (ssa:asa)	1,1′- (*syn*:*anti*)	isolated yield[c]
1	**61as**	6 d	>95:5	>95:5	75%
2	**124s**[d]	2 d	(62:38)[e,j]	NA[i]	18%[f,h]
3	**113as**	6 d	>95:5	>95:5	84%
4	**117sss**	3 d	60:40	>95:5	81%
5	**81ass** (Pg = TES)	3 d	55:46	>95:5	79%
6	**81ass** (Pg = MOM)	3 d	(50:50)[g]	>95:5	50%[h]

[a]Determined by ^{1}H NMR of the crude reaction mixture; >95% conversions were obtained with 10-15% of the retroaldol products (aldehyde and ketones). [b]Equilibrium was confirmed by subjecting the mixture of diastereomers to the same reaction conditions. [c]Combined isolated yields of the indicated mixture of diastereomers. [d]A 5:1 mixture of **124s** and **124a** was used as the starting material; except ^{1}H NMR, no other characterization data were obtained for these aldol adducts. [e]Ratio obtained after three cycles. [f]Yield after three cycles. [g]Structures of **81ssa** (Pg = MOM) and **81asa** (Pg = MOM) are tentatively assigned. [h]Low yield due to more side products and incomplete isomerization. [i]Not Applicable. [j]Ratio of **124a** and **124s**, respectively.

Having success in the isomerizations of Mg(II) aldolates of achiral ketones under the newly optimized conditions, the next goal was to perform the isomerization of Mg(II) aldolates of chiral ketones. Aldol adducts **117sss**, **81ass** (Pg = TES) and **81ass** (Pg = MOM) were selected for further investigation. Each of these aldols was subjected to the standard conditions and the results are summarized in Table 2.24 (entries 4-6). Isomerizations of Mg(II) aldolates of chiral ketones were found to be faster than those of achiral ketones (entries 4-6 versus entries 1-3). A reaction time of three days was found to be optimal for complete isomerization and a ~50:50 mixture of two 1′,2′-*anti* (non-Felkin) aldol adducts was obtained. The TES-protected aldols **117sss**, **81ass** (Pg = TES) afforded higher yields than the MOM-protected aldol **81ass** (Pg = MOM) (entries 4 and 5 versus entry 6). Therefore, TES-protected substrates were used for further study.

2.3.4.6. Effects of the aldehyde fragment of the starting aldol on isomerization

Isomerization of Mg(II) aldolates of the compounds listed in Table 2.24 provided 1,1′-*syn* aldols as the exclusive products. In contrast, 1,1′-*anti* aldols were obtained as the major products in isomerization of BrMg(II) aldolates of all the examples reported the literature (Scheme 2.17).[132-133, 147, 152] It was hypothesized that the structure of the aldehyde plays an important role in the observed 1,1′-*syn* selectivity. To explore this structure-selectivity relationship, isomerization of aldol adducts derived from various aldehydes were investigated. A major challenge in this study was identification of the final products. Analysis of the ^{1}H NMR spectrum becomes challenging, especially when all possible aldol diastereomers are not known. To mitigate this problem, aldol adducts of achiral ketones, 3-pentanone (R = H) and 2-methyl-3-pentanone (R = Me) where most (if not all) of the diastereomers are known, were selected (Figure 2.9).

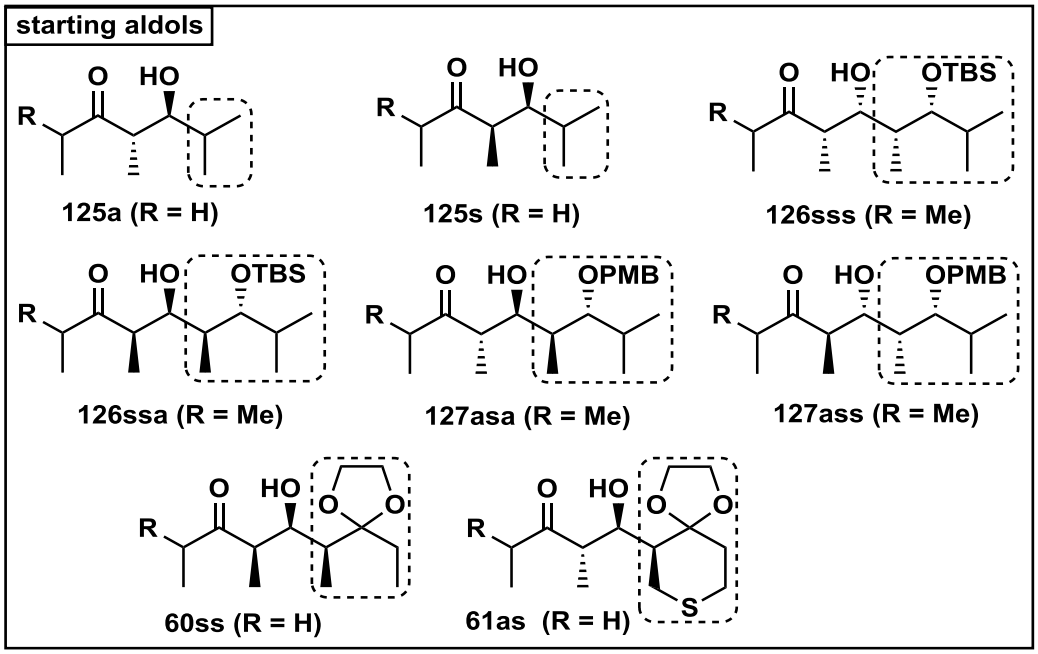
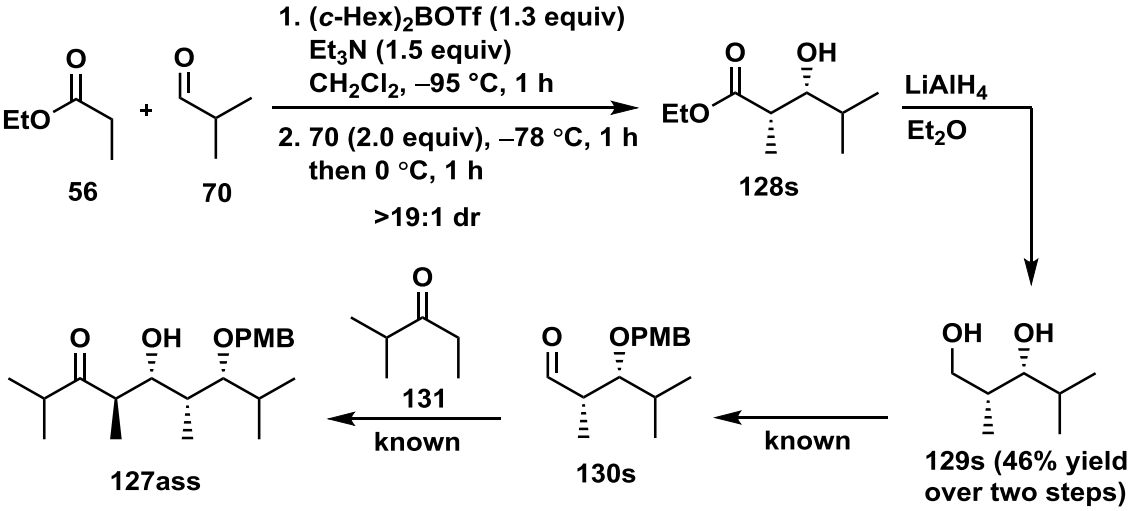


Figure 2.9. Aldol adducts selected to probe the role of the aldehyde fragment on isomerization selectivity.

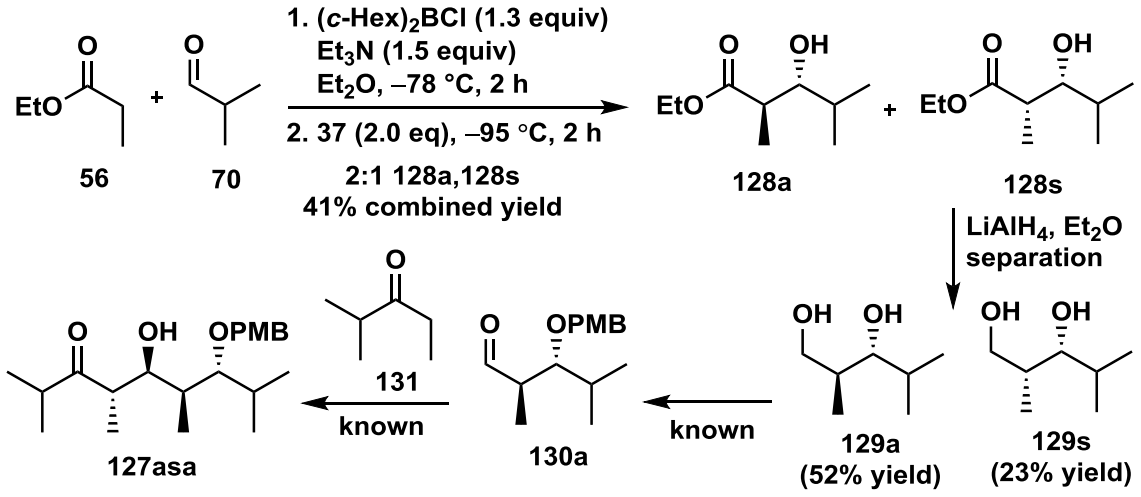
To simplify the syntheses of the selected aldol adducts (Figure 2.9), racemic aldols were used. Following the reported[106] procedure, a 12:1 mixture of **125s**[106] and **125a**[133] was obtained and the mixture was used directly in the isomerization study. Enantioselective syntheses of **126sss**,[53] **126ssa**,[53] **127asa**[85] and **127ass**[85] have been reported by Evans *et al*.; however, preparation of these compounds in racemic form is not reported in the literature. To avoid problems with diastereomer separation, the initial goal was to access **128a** and **128s** (Scheme 2.23) as single isomers (ca. >19:1 dr). Abiko *et al*.[153] reported the reaction of ethyl propionate (**56**) with (*c*-Hex)$_2$BOTf and Et_3N followed by addition isobutyraldehyde (**70**) and a single isomer **128a** was obtained with >19:1 dr. Following the general procedure reported by Abiko *et al*.,[153] the reaction of **56** with **70** afforded a single isomer **128s** (instead of **128a**) with >19:1 dr (Scheme 2.23). Reduction of the crude reaction mixture with $LiAlH_4$ provided diol **129s**[106] as a diastereomerically pure compound. Diol **128s** was converted to **127ass**.[106]

Scheme 2.23. Preparation of **130s** and **127ass**.



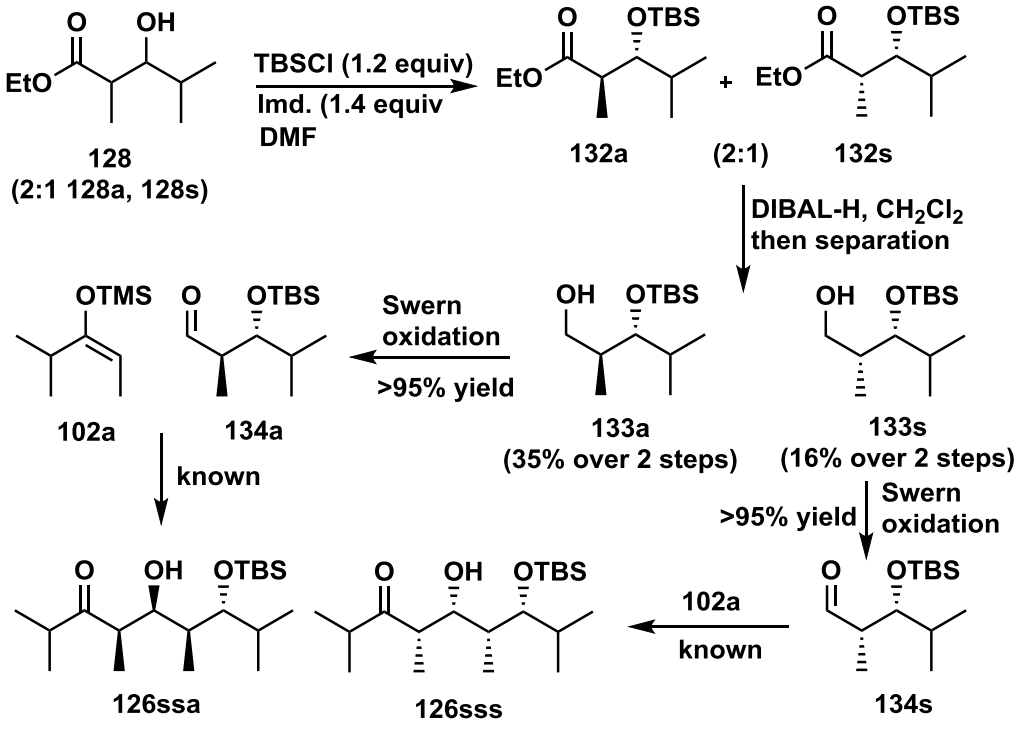
To have selective access to **128a**, aldol coupling of **70** with the (*E*)-enol dicyclohexylborinate of **56** was attempted. A brief optimization study afforded conditions suitable to access **128a** in acceptable yield and diastereoselectivity (Scheme 2.24). Unfortunately, the aldol diastereomers **128a** and **128s** could not be separated at this stage. Consequently, the mixture of was reduced to **129a** and **129s** that were isolated in diastereomerically pure form. Diol **129a** was then converted to **127asa**.[85]

Scheme 2.24. Preparation of **130a** and **127asa**.



For the preparation of **134a** and **134s** (Scheme 2.25), the ~2:1 mixture of **128a** and **128s** was converted into the corresponding mixture of TBS ethers **132a** and **132s** that were reduced according to the procedure reported by Reynolds *et al*.[154] After separation, **133a** and **133s** were converted to **126ssa** and **126sss**, respectively.[53]

Scheme 2.25. Preparation of **126ssa** and **126sss**.



Aldol adducts depicted in Figure 2.9 were categorized into two groups: aldols **125** and **126** that do not possess an oxygen atom at the C-3′ position (**125**) or the oxygen atom is masked by a bulky TBS group (**126**) and aldols **60** and **61** and **127** which possess an oxygen atom(s) at the C-3′ position — capable of intramolecular coordination with Mg(II) aldolate. It was hypothesized that the equilibration of Mg(II) aldolates of **125-126** would provide the 1,1′-*anti* diastereomers as the major product because aldolate **135a** was expected to be more stable than **135s** (Figure 2.10). Aldolate **135a** has both the substituents at C-1 (Me) and C-1′ (*i*-Pr) in pseudo-equatorial orientations. In contrast, one of the substituents in **135s** is in an axial orientation and therefore, suffers from a gauche interaction. This hypothesis was further supported by the results reported in the literature (Scheme 2.17).[132-133, 147, 149] Isomerizations of Mg(II) aldolates of **60-61** and **127** were expected to provide the 1,1′-*syn* diastereomers as the major products because aldolates like **136sa**

would be more stable than aldolates like **136aa**. Aldolate **136aa** suffers from a *syn*-pentane interaction between Me at C-1 and CH_2 at C-2′. The 1′,2′-*syn* diastereomers **136ss** and **136as** were also expected to be less stable than **136sa** because of the axial orientation of the C-2′ substituent.

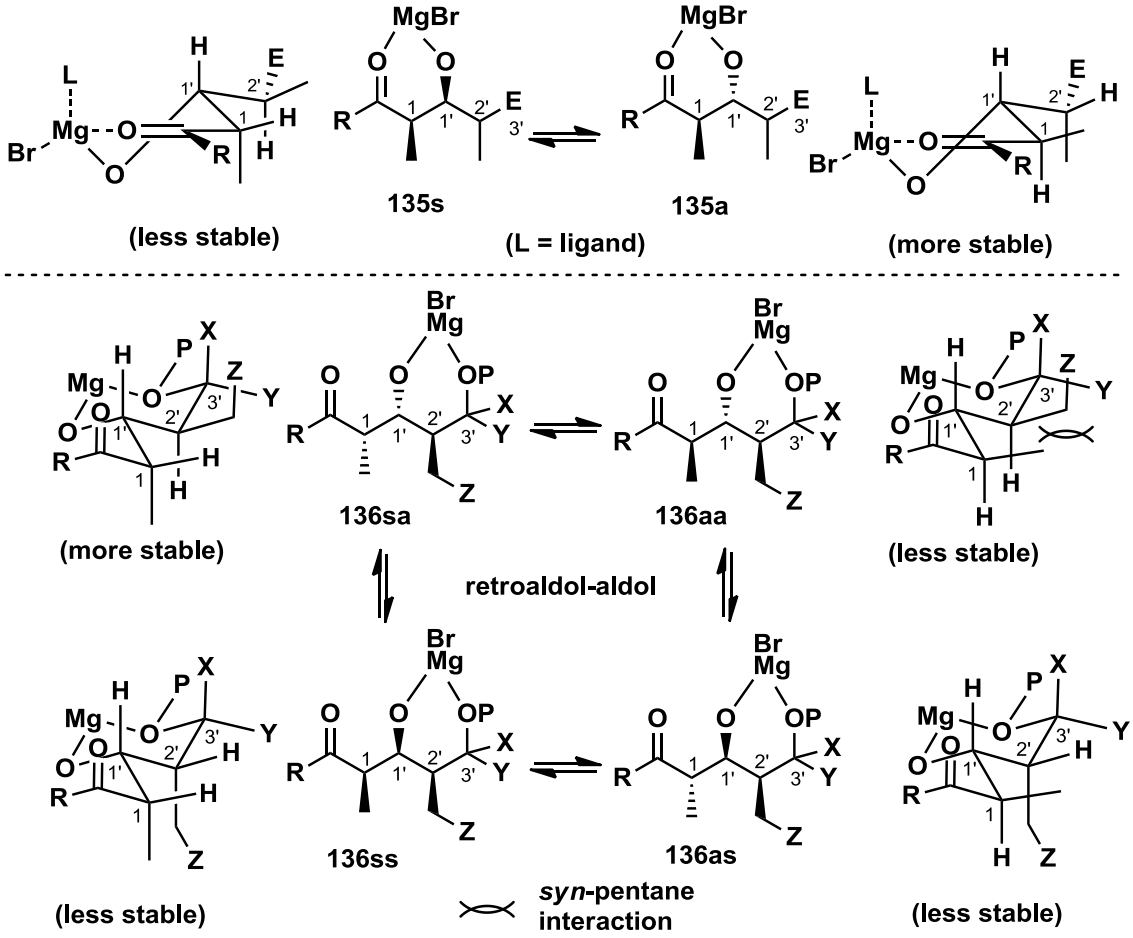


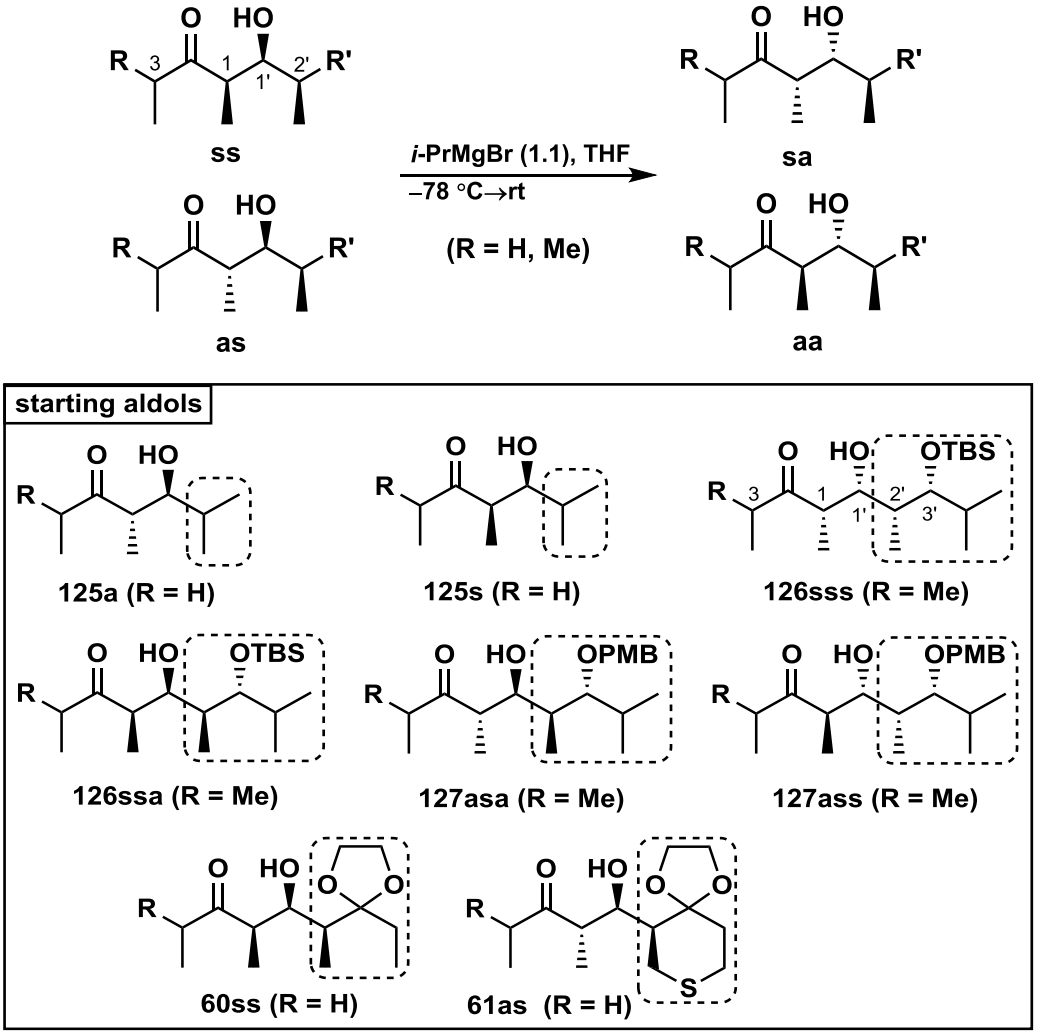
Figure 2.10. Proposed rationale for the origin of 1,1′-*syn*-1′,2′-*anti* (**sa**) selectivity.

To test this hypothesis the aldol adducts shown in Figure 2.9 were subjected to the standard isomerization conditions and the results are summarized in Table 2.25. Equilibrium was confirmed by subjecting the indicated mixture of aldol adducts to the same reaction conditions; no detectable change was observed. Isomerization of BrMg(II) aldolates of **125s** was reported in the literature (see Scheme 2.17) and known to provide a 9:91 mixture of **125a** and **125s**, respectively.[133] When either **125a** or **125s** was treated with *i*-PrMgBr under the optimized conditions, a 10:90 mixture of **125a** and **125s** was obtained (entries 1 and 2), consistent with the literature finding.[133] Isomerization Mg(II) aldolates of **126sss** and **126ssa** provided all four possible

aldol adducts (entries 3and 4). As expected, both **126sss** and **126ssa** provided 1,1′-*anti* aldols (≥84%) as the major products. The ratio of 1′,2′-*anti* (non-Felkin) and 1′,2′-*syn* (Felkin) aldols for both **126sss** and **126ssa** were ~1:1, suggesting no significant effect from the 2′,3′-*anti* versus 2′,3′-*syn* relative configurations.

The relative amount of 1,1′-*syn* aldols was significantly higher when **127asa** was subjected to isomerization, though 1,1′-*anti* aldols remained the major products. Additionally, a low ratio of 1′,2′-*anti* (non-Felkin) and 1′,2′-*syn* (Felkin) aldols was obtained. Interestingly, the selectivity reversed (from favoring 1′,2′-*syn* to 1′,2′-*anti*) when **127ass** was subjected to isomerization (entry 6), providing 91% of 1′,2′-*anti* (non-Felkin) aldol adducts. As anticipated, the ratio of 1′,2′-*anti* (non-Felkin) and 1′,2′-*syn* (Felkin) aldols was also dramatically improved, providing 91% of the 1′,2′-*anti* (non-Felkin) aldols. Of this 91%, 86% was a single isomer with the 1,1′-*syn*-1′,2′-*anti* (sa) relative configuration. Comparison of entries 5 and 6 showed that the 2′,3′-relative configuration of **127asa** and **127ass** had strong influence on the observed diastereoselectivity (*cf*. Figure 2.10). Isomerization of **60ss** afforded only two of four possible aldol adducts (entry 7). Once again, the major product has 1,1′-*syn*-1′,2′-*anti* (sa) relative configuration. Isomerization of **61as** provided a single diastereomer again with the 1,1′-*syn*-1′,2′-*anti* (sa) relative configuration (entry 8). Comparison of entries 1-4 with entries 5-8 (Table 2.25) suggests that the nature of the C-7 oxygen atom(s) allows either 1′,2′-*anti* (non-Felkin) or 1′,2′-*syn* (Felkin) aldols to be the major or exclusive product. Aldol **61as**, derived from **29a**, provided the best diastereoselectivity. Consequently, aldols of **29a** were used for further investigation.

Table 2.25. Isomerization of Mg(II) aldolates of aldol adducts with varying aldehyde strcuture.



entry	starting aldol	time	equilibrium ratio[a,b] (ss:sa:as:aa)	1,1′-*syn*: 1,1′-*anti* aldols[i]	isolated yield[c]
1	**125a**	2 h	10:90	10:90	ND[g]
2	**125s**[h]	2 h	11:89	11:89	ND[g]
3	**126ssa**	1 h	7:5:47:41	12:88	75%
4	**126sss**	1 h	11:5:42:42	16:84	70%
5	**127asa**	1 d	19:15:41:25	34:66	70%
6	**127ass**	8 h	3:86:6:5	89:11	76%[d]
7	**60ss**	6 d[f]	0:70:30:0	70:30	73%

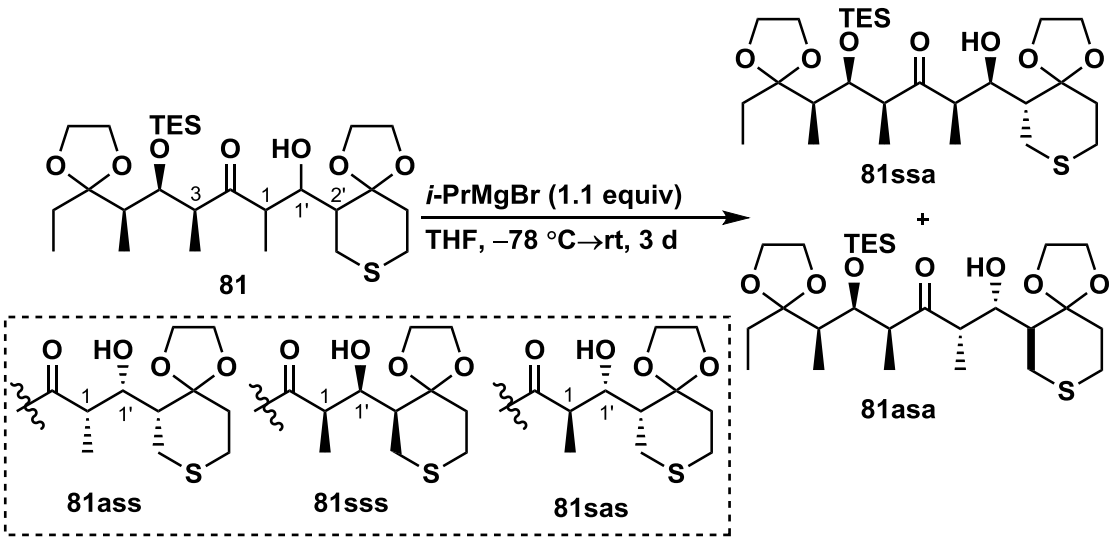
8	**61as**	6 d	>95:5	>95:5	75%[d]

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Equilibrium was confirmed by subjecting the mixture to the same reaction conditions. [c]Isolated yields of indicated mixtures. [d]Isolated yield of **sa**. [f]After two cycles. [g]Not determined. [h]A 12:1 mixture of **125s** and **125a** was used as starting material. [i]Refers to the ratio Σ(**ss**+**as**) to Σ(**sa**+**aa**).

Isomerization of Mg(II) aldolates derived from aldol adducts of chiral ethyl ketones and aldehyde **29a** provided 1′,2′-*anti* (non-Felkin) aldols as the exclusive product (Table 2.24). Only two of the eight possible diastereomers were detected and these were isolated in good yields. The TES-protected aldols **81** (*cf*. entry 5, Table 2.24) were selected for further investigation because the corresponding 1′,2′-*anti* (non-Felkin) aldols were unobtainable via directed aldol couplings.

To firmly establish the equilibrium ratio, various 1′,2′-*syn* (Felkin) aldol diastereomers (**81ass**, **81sss** and **81sas**) from coupling ketone **62b** and **29a** were prepared by AR2P (see section 2.2.). It was hypothesized that retroaldol of the corresponding Mg(II) aldolates of each of these diastereomers would result in the formation of the same Mg(II) enolate (as a mixture of *E* and *Z*) and aldehyde. Consequently, complete equilibration of the corresponding Mg(II) aldolates should afford the same diastereomeric ratios. In each case, two 1′,2′-*anti* (non-Felkin) diastereomers (**81ssa** and **81asa**) were formed as the final products in ~1:1 diastereomeric ratios (entries 1-3, Table 2.26).

Table 2.26. Isomerization of Mg(II) aldolates of different diastereomers of aldol **81**.

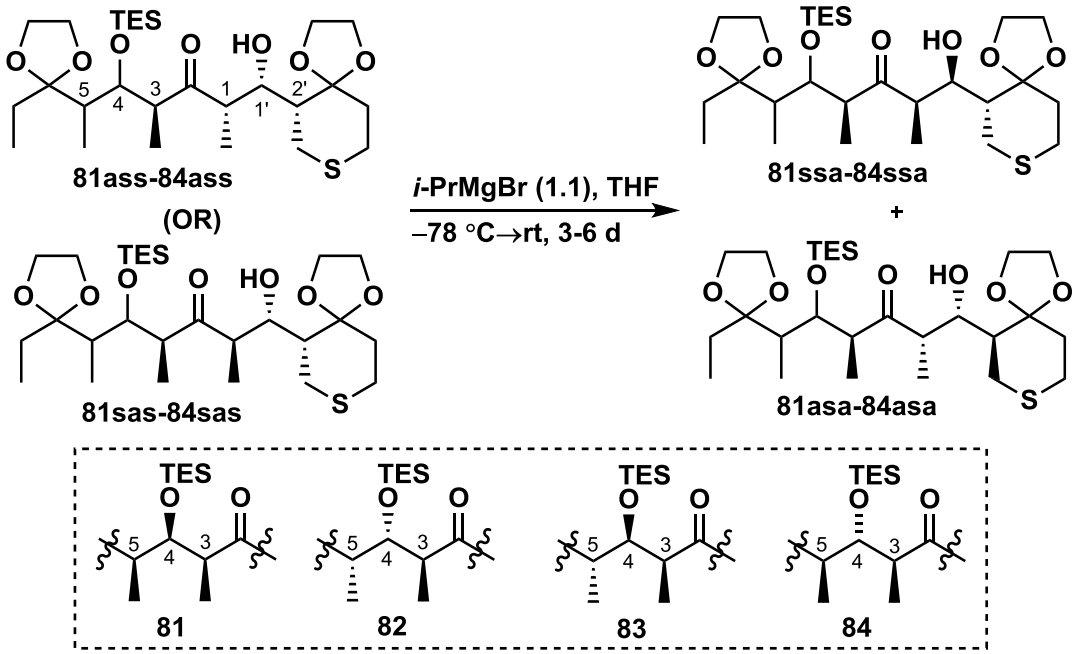


entry	starting aldol	(81ssa:81asa)[a]	isolated yield[b]
1	**81ass**	53:47	82
2	**81sss**	50:50	79
3	**81sas**	52:48	80
4[c]	**81ssa**	73:27	75
5[c]	**81asa**[d]	28:72	71

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Isolated yields of the indicated mixture of aldols. [c]Reaction was conducted for 5 d. [d]A 83:17 mixture of **81asa** and **81ssa** was used as starting material.

Attempted isomerization of diastereomers **81ssa** and **81asa** was found to be extremely slow under the standard isomerization conditions (entries 4 and 5, Table 2.26). Equilibrium could not be reached even after 6 days at room temperature. These results suggest that the Mg(II) aldolates of 1′,2′-*anti* (non-Felkin) diastereomers (e.g., **81ssa** and **81asa**) are significantly more stable than those of the corresponding 1′,2′-*syn* (Felkin) diastereomers (e.g., **81ass, 81sss** and **81sas**).

Table 2.27. Equilibrium study with two different aldol diastereomers as the starting material.



entry	starting aldol	time (d)	equilibrium ratio[a,b] (ssa:asa)	isolated yield[c]
1	**81ass**	3	55:45	81%
2	**81sas**	3	49:51	80%
3	**82ass**	3	63:37	81%
4	**82sas**	3	53:47	83%
5	**83ass**	3[d]	61:39	80%
6	**83sas**	6	67:33	69%
7	**84ass**	3	41:59	78%
8	**84sas**	6	39:61	74%

[a]Determined by ^{1}H NMR of the crude reaction mixture; >95% conversions were obtained with 10-15% of the retroaldol products (aldehyde and ketones). [b]Equilibrium was confirmed by subjecting the mixture of diastereomers to the same reaction conditions. [c]Combined isolated yields of the indicated mixture of diastereomers. [d]The crude material was resubjected under the same reaction conditions.

To determine the effect of the 3,4- and 4,5-relative configurations on the equilibrium ratio, racemic aldol adducts from diastereomeric ketones with four possible 3,4- and 4,5-relative

configurations were prepared by AR2P (see section 2.3.3). The 1,3-*anti*-1,1′-*syn*-1′,2′-*syn* (**ass**) and 1,3-*syn*-1,1′-*anti*-1′,2′-*syn* (**sas**) aldols were chosen for study due to their ease of preparation. Each of these diastereomers was subjected to the standard isomerization conditions (Table 2.27). Equilibrium was confirmed by resubjecting the indicated mixture of aldol adducts to the same reaction conditions; no detectable change was observed. In all cases, only two of the eight possible diastereomers were detected with diastereomeric ratios ranging from 1:1 to 1.7:1. Both diastereomers had 1,1′-*syn*-1′,2′-*anti* (sa) relative configurations; however, one had 1,3-*syn* (for **ssa**) and the other had 1,3-*anti* (for **asa**) relative configuration (see section 2.3.5.).

2.3.4.7. Isomerization of Mg(II) aldolates of enantioenriched aldol adducts

Analysis of the structures for the two 1′,2′-*anti* (non-Felkin) aldol products **ssa** and **asa** (Table 2.27) obtained from isomerization shows that the two products result from different combinations of reactant enantiomers (ketone and aldehyde). As shown in Figure 2.11, **137ssa** and **137asa** have different relative configurations at C-3 and C-2′ (*R*,*R* vs. *S*,*R*). Comparing the relative configurations of the C-3 and C-2′ stereocenters in **137sas** and **137ssa**, it was apparent that the latter originated from the former via retroaldol-aldol isomerization, perhaps without dissociation of the enolate-aldehyde complex. A retroaldol reaction of racemic **137sas** would form enolate (*R*)-**19b** and aldehyde (*S*)-**29a** (and (*S*)-**19b** and (*R*)-**29a**). Aldol coupling of these reactant pairs would result in formation of racemic **137ssa** with retention of the absolute configurations at C-3 and C-2′. However, the formation **137asa** from **137sas** must result from the aldol coupling of (*R*)-**19b** with (*R*)-**29a** (and (*S*)-**19b** with (*S*)-**29a**) and this can be explained by crossover between the *in situ* generated retroaldol fragments.

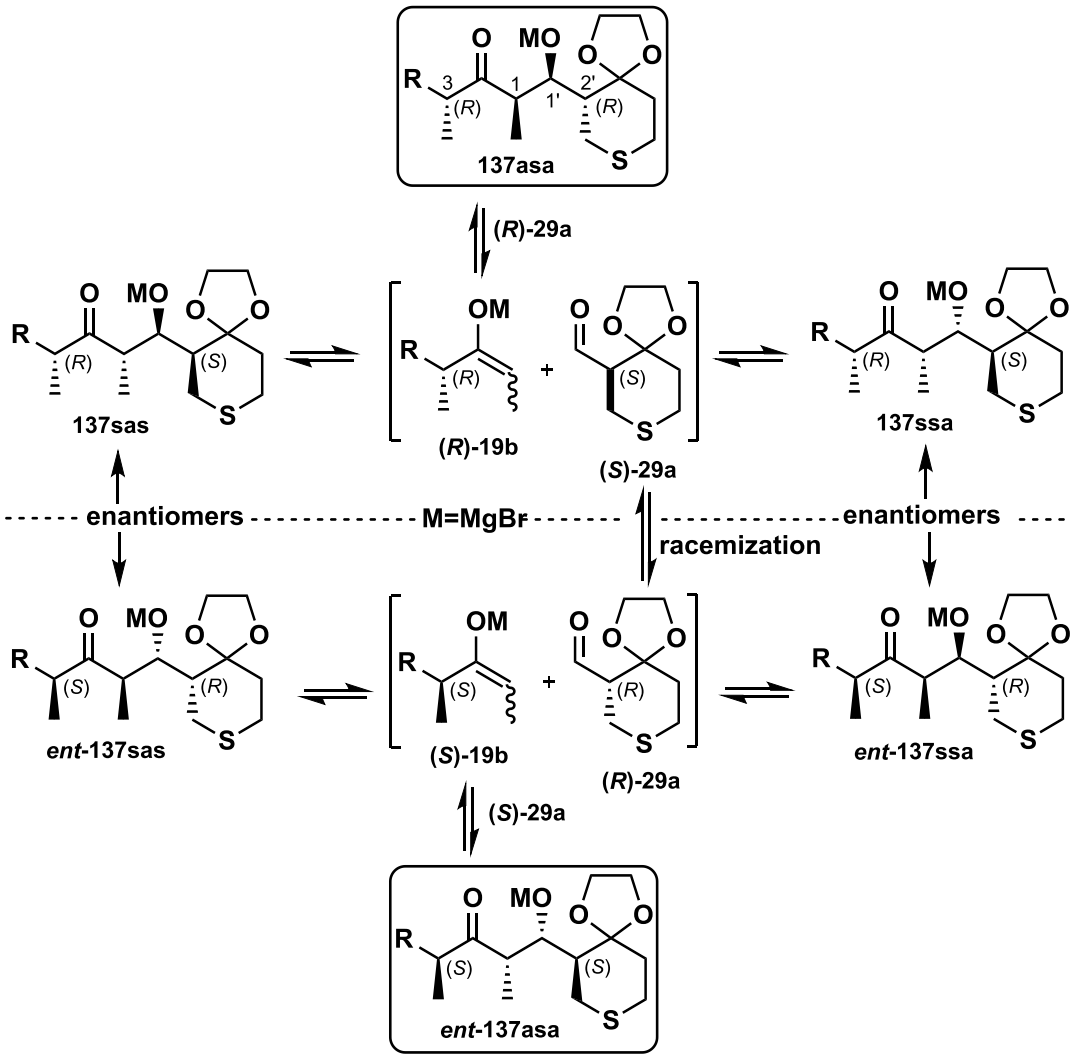
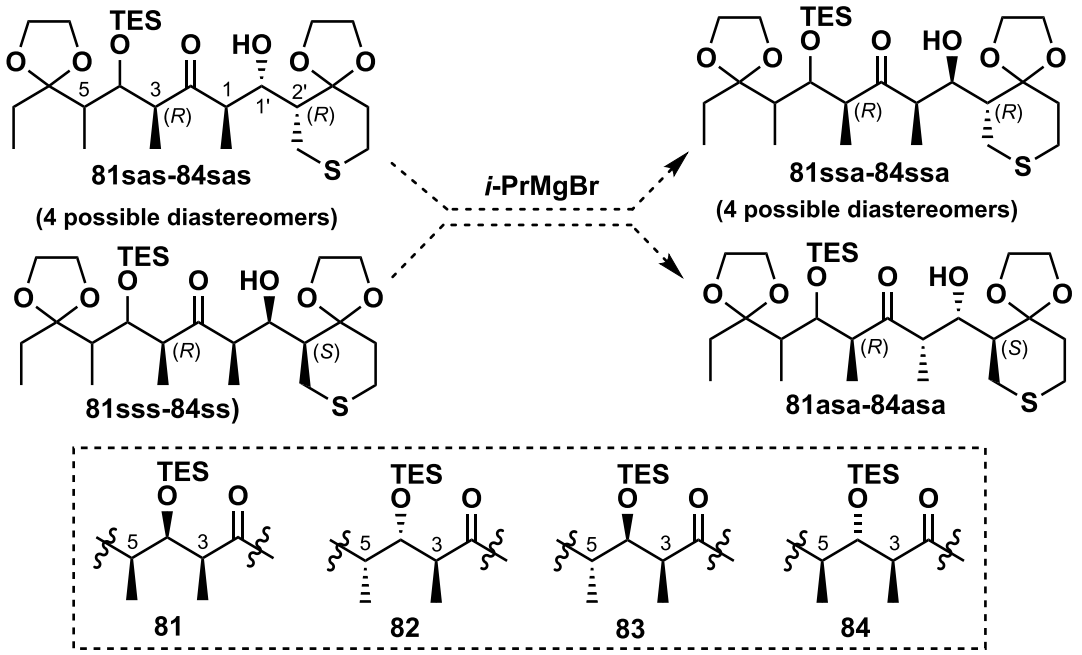


Figure 2.11. Proposed rationale for the formation of **137ssa** and **137asa**.

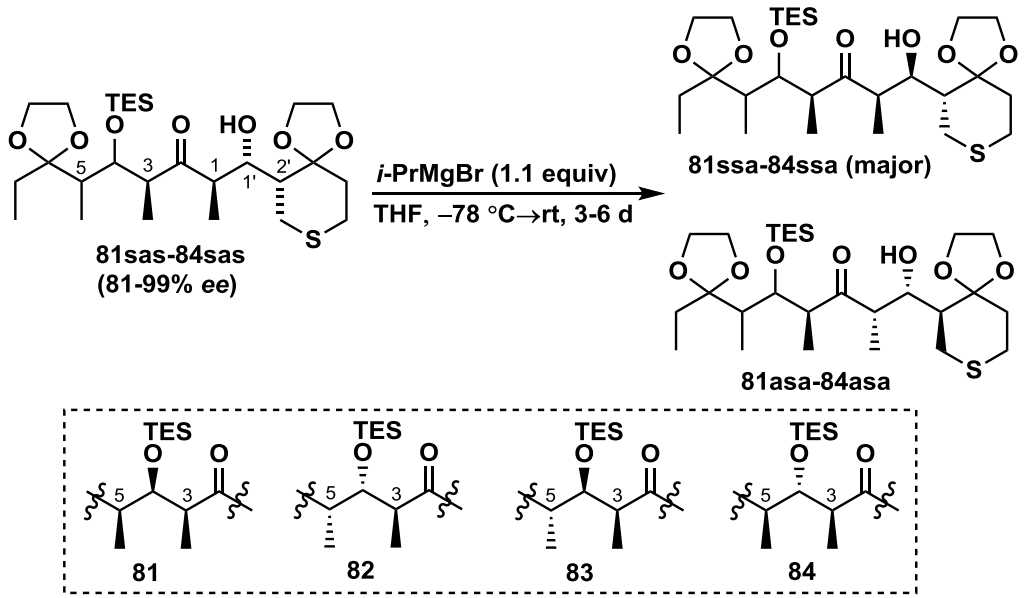
It was hypothesized that only one of two non-Felkin aldols (e.g., **137ssa**) would be formed if an enantiopure aldol adduct (**137sas**) is used. The absence of the other enantiomer (***ent*-137sas**) would avoid the formation of the crossover products (***ent*-137ssa**, **137asa**, and ***ent*-137asa**), provided that the rate of retroaldol-aldol reactions is significantly faster than the rate of racemization of *in situ* formed enantiopure aldehyde ((*S*)-**29a**). It has been reported in the literature that enantiopure **29a** is highly susceptible to racemization.[110] Racemization of (*S*)-**29a** would enable the formation of **137asa**. The presence of **137asa** among the products of isomerization of enantiopure **137sas** and similarly, the formation of **137ssa** from isomerization of enantiopure **137sss** are direct measurements of the extent of racemization of the *in situ* formed enantiopure aldehyde (**29a**).

Scheme 2.26. Selection of starting materials to access enantiopure **ssa** and **asa**.



To have selective access to enantioenriched **ssa** and **asa** (Scheme 2.26), the starting aldols were selected based on the criteria that the absolute configurations of the C-3 and C-2′ stereocenters of the enantiopure starting aldol be retained in the product (see Figure 2.11). In principle, any diastereomer of the starting aldol with desired absolute configurations at C-3 and C-2′ stereocenters can be used, provided a method to access these diastereomers in non-racemic form is available. The **sas** and **sss** diastereomers were chosen to access the **ssa** and **asa** diastereomers, respectively, because both diastereomers **sas** and **sss** can be enantioselectively accessed by AR2P (see section 2.2.).

Table 2.28. Stereoselective access to enantioenriched **81ssa-84ssa**.



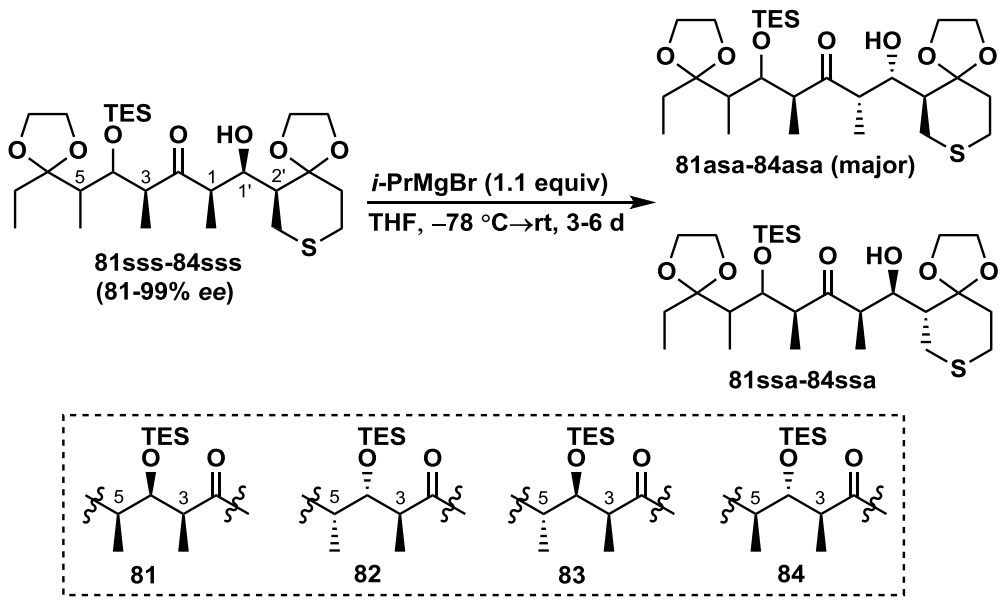
entry	starting aldol (*ee*)	time (d)	products	(ssa:asa)[a,b]	isolated yield[c]
1	**(−)-81sas** (99%)	3	**(+)-81ssa, (+)-81asa**	86:14	72%
2	**(+)-82sas** (99%)	3	**(+)-82ssa, (+)-82asa**	95:5	86%
3	**(−)-83sas** (81%)	6	**(+)-83ssa, (−)-83asa**	83:17	57%[d]
4	**(+)-*ent*-84sas** (81%)	6	**(−)-84ssa, (−)-84asa**	86:14	59%[d]

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Also contains <10% of retroaldol products. [c]Isolated yields of the major diastereomer. [d]Lower yields due to more byproducts (elimination and interrupted retroaldol products).

The enantioenriched aldols **81sas-84sas** were subjected to isomerization conditions similar to those used for the corresponding racemic aldol adducts (*cf.* Table 2.27) and the results are summarized in Table 2.28. No starting materials were detected by ^{1}H NMR of the crude reaction mixtures after the indicated reaction time. Only two of eight possible diastereomers were detected in all cases. Both **(+)-82sas** and **(−)-81sas** had a faster rate of isomerization than **(−)-83sas** and **(+)-*ent*-84sas** (compare entries 1 and 2 with entries 3 and 4). The increased reaction time for **(−)-83sas** and **(+)-*ent*-84sas** resulted in lower yields of the desired aldol adducts due to increased amounts of byproducts (e.g., OTES elimination and interrupted retroaldol products; i.e., the corresponding ketones and aldehyde). Isomerization of the Mg(II) aldolate of **(+)-82sas** provided

excellent diastereoselectivity (entry 2). Moderate diastereoselectivities (4.9-6.1:1) were obtained in other cases (entries 1, 3, and 4). Low diastereoselectivity obtained in isomerization of **(−)-81sas** indicate that a significant amount of racemization occurred under the reaction conditions. The low diastereoselectivities obtained in isomerizations of **(−)-83sas** and **(+)-*ent*-84sas** are in part due to the low enantiopurities (81% *ee*′s) of the starting materials. Starting materials with low enantiopurities not only provide products with similar enantiopurities but also provide a source of the enantiomer of the *in situ* formed aldehyde, resulting an increased amount of the minor 1′,2′-*anti* (non-Felkin) diastereomer during isomerization (*cf*. Figure 2.11). Because the starting materials for entries 3 and 4 (Table 2.28) have 90% enantiopurity (i.e., 81% *ee*), it contains 10% of the undesired enantiomer which leads to the formation of 10% of the undesired **asa** diastereomer after isomerization, resulting in overall increase in the amount of **asa** and lowering the ratios of **ssa** and **asa**. Therefore, higher diastereoselectivities are expected in isomerizations of more enantiopure **(−)-83sas** and **(+)-*ent*-84sas**.

Table 2.29. Stereoselective access to enantioenriched **81asa-84asa**.



entry	starting aldol (*ee*)	time (d)	products	(asa:ssa)[a,b]	isolated yield[c]
1	**(+)-81sss** (99%)	3	**(+)-81asa**, **(+)-81ssa**	>95:5	70%
2	**(+)-82sss** (99%)	3	**(+)-82asa**, **(+)-82ssa**	>95:5	81%

3	**(−)-83sss** (81%)	6	**(−)-83asa**, **(+)-83ssa**	75:25	54%[d]
4	**(−)-*ent*-84sss** (81%)	3	**(−)-84asa**, **(−)-84ssa**	82:18	57%[d,e]

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Also contains <10% of retroaldol products. [c]Isolated yields of the major diastereomer. [d]Lower yields due to more byproducts (elimination and interrupted retroaldol products). [e]A 1.5:1 mixture of **(−)-84ssa** and **(−)-84asa** was also isolated in 23% yield.

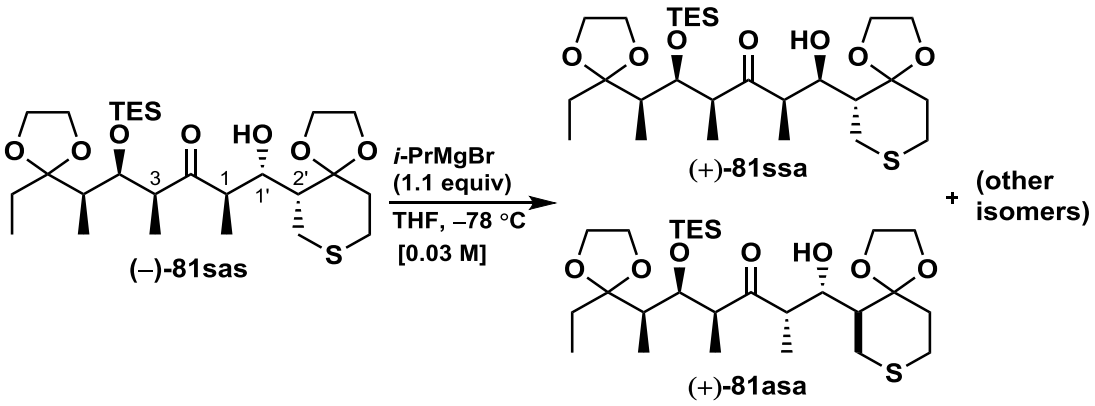
Enantioenriched **81sss-84sss** were also subjected the isomerization conditions similar to those used for racemic **81ass-84ass** (see Table 2.27) and the results are summarized in Table 2.29. It was expected that **81sss-84sss** would require isomerization times similar to those for **81ass-84ass** because both have the 1,1′-*syn*-1′,2′-*syn* (ss) relative configurations and the reaction times required for isomerizations of diastereomers **81ass** and **81sss** were found to be identical (*cf*. entries 1 and 2, Table 2.26). The starting aldols were consumed after the indicated reaction times. Only two of eight possible diastereomers were detected in all cases with moderate to excellent diastereoselectivities (75:25 to 95:5 dr). The increased reaction time for isomerization of Mg(II) aldolate of **(−)-83sss** resulted in increased amounts of byproducts, lowering overall yield of the desired **(−)-83asa** (entry 3). No significant racemization was observed in the isomerizations of Mg(II) aldolates of **(+)-81sss** and **(+)-82sss**, resulting in high diastereomeric ratios (entries 1 and 2). Moderate diastereoselectivities were obtained in isomerization of Mg(II) aldolates of **(−)-83sss** and **(−)-*ent*-84sss**. The lower diastereoselectivities are partly due to the low enantiopurities (81% *ee*′s) of the starting materials (entries 3 and 4, Table 2.29). Therefore, higher diastereoselectivities are expected in isomerizations of more enantiopure **(−)-83sss** and **(−)-*ent*-84sss**.

2.3.4.8. Isomerization study at lower temperature

Although the isomerizations of enantioenriched aldol adducts provided moderate to excellent diastereoselectivities in favor of the desired 1′,2′-*anti* (non-Felkin) diastereomer (Tables 2.28-2.29), in some cases, significant racemization of the *in situ* formed aldehyde was also observed (indicated by the presence of the minor 1′,2′-*anti* (non-Felkin) diastereomer). For instance, the presence of 14% of the undesired **(+)-81asa** was detected in isomerization of Mg(II) aldolate of **(−)-81sas** (entry 1, Table 2.28). Because **(−)-81sas** had 99% *ee*, the **(+)-81asa** diastereomer must have resulted from the racemization of the *in situ* formed aldehyde ((*R*)-**29a**, see Figure 2.11). It was hypothesized that decreasing the reaction temperature may decelerate the

racemization (more than retroaldol-aldol isomerization) and improve the diastereoselectivity. Toward that end, isomerization was investigated at lower temperatures and the results are presented below.

Table 2.30. Variation of temperature and time in isomerization of Mg(II) aldolate of **(−)-81sas**.



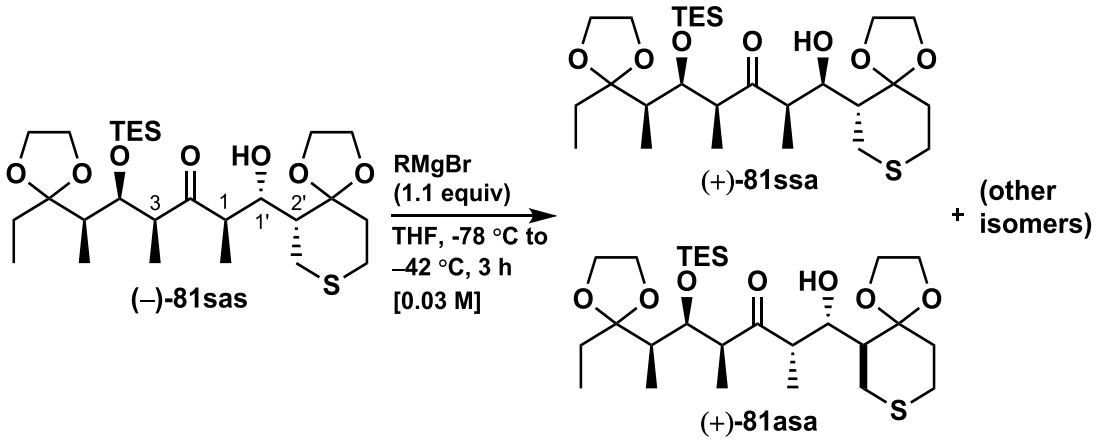
entry	conditions	(−)-81sas[a] (%)	(+)-81ssa[a]:(+)-81asa[a]:Σ[a,b] (%)	byproducts[a,c] (%)
1	−42 °C, 0.25 h	50	19:2:29	ND[d]
2	−42 °C, 1 h	50	26:2:22	ND[d]
3	−42 °C, 3 h	48	28:5:19	ND[d]
4	−20 °C, 3 h	33	33:6:23	5
5	−20 °C, 6	40	24:5:27	4
6	0 °C, 3 h	20	40:10:23	7
7	0 °C, 6 h	23	40:7:24	6

[a]Mole percent determined from ^{1}H NMR of the crude reaction mixture after normalization. [b]Represents the sum of other isomers detected (**81ass**, **81sss** and **81aaa**). [c]Byproducts contain **62b** and OTES elimination products. [d]Not detected.

The reaction of **(−)-81sas** with *i*-PrMgBr at −42 °C consumed 50% of the starting material within 15 min (entry 1, Table 2.30). Among the new diastereomers formed, 20% was the desired **(+)-81ssa**. An increase in reaction time did not improve conversion but significantly changed the product distribution (compare entry 1 with entries 2 and 3). An increase in temperature

improved the conversion (entries 5-7). Elimination of the OTES group was observed when the reaction was performed at 0 °C. The lack of a significant change in conversion with increasing reaction time was surprising given the conversion increased at increased temperatures. One possible reason is that the Grignard (*i*-PrMgBr), or the Mg(II) aldolates, or both might be forming aggregates at lower temperatures.[155-156] To probe this hypothesis, variations to the Grignard reagents (Table 2.31) and concentrations (Table 2.32) were made.

Table 2.31. Variation of Grignard reagent in isomerization of Mg(II) aldolate of **(−)-81sas**.



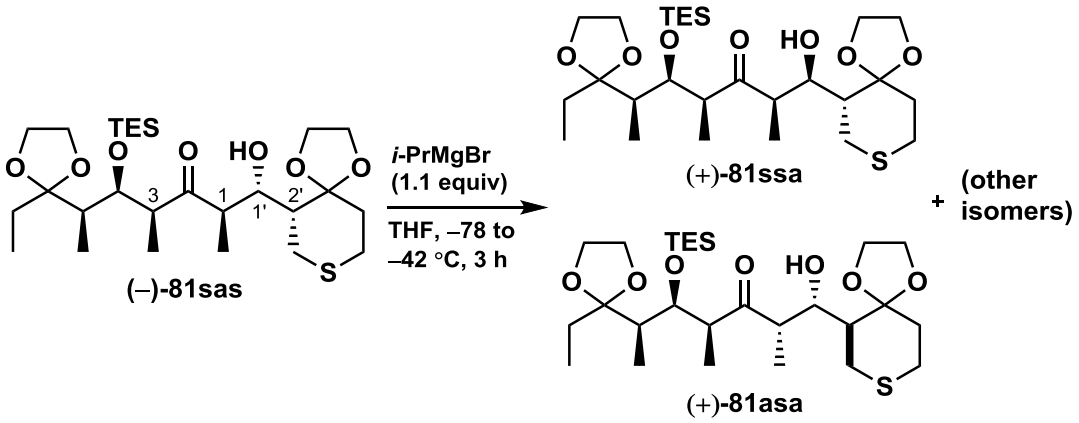
entry	RMgBr	(−)-81sas[a] (%)	(+)-81ssa[a]; (+)-81asa[a]:Σ[a,b] (%)	byproducts[a,c] (%)
1	*i*-PrMgBr	48	28:5:19	ND[d]
2[e]	*i*-PrMgCl	66	14:1:18	1
3[f]	*t*-BuMgBr	53	11:9:27	ND[d]
4[f]	*t*-BuMgCl	86	2:0:12	ND[d]
5	PhMgBr	51	26:2:21	ND[d]

[a]Mole percent determined from ^{1}H NMR of the crude reaction mixture after normalization. [b]Represents the sum of other isomers detected (**81ass**, **81sss** and **81aaa**). [c]Byproducts contain **62b** and OTES elimination products. [d]Not detected. [e]Reaction was performed at 0 °C for 0.5 h. [f]Reaction was performed with racemic substrate.

Conversions obtained using aryl- or alkylmagnesium bromides (RMgBr; entries 1, 3, and 5) were higher than those obtained using alkylmagnesium chlorides (RMgCl; entries 2 and 4).

This may be directly correlated to the reactivity of Grignard reagents used or the resulting Mg(II) aldolates formed after deprotonation. The reaction with PhMgBr provided conversion that is comparable with the conversion obtained with *i*-PrMgBr (entries 1 and 5). A lower conversion was obtained with *t*-BuMgBr (entry 3). Irrespective of the Grignard used, the conversion could not be improved beyond 52% under these conditions. As shown in Table 2.31, among the various Grignard reagents screened for isomerization, *i*-PrMgBr was found to be superior, affording highest conversion (52%) and highest amount of the desired 1′,2′-*anti* (non-Felkin) aldols (33%). Consequently, *i*-PrMgBr was used for all subsequent reactions.

Table 2.32. Variation of concentration in isomerization of Mg(II) aldolate of **(−)-81sas**.



entry	conc	(−)-81sas[a] (%)	(+)-81ssa[a]: (+)-81asa[a]:Σ[a,b] (%)	byproducts[a,c] (%)
1	0.017 M	59	18:2:21	ND[d]
2	0.034 M	48	28:5:19	ND[d]
3	0.068 M	57	18:3:19	3

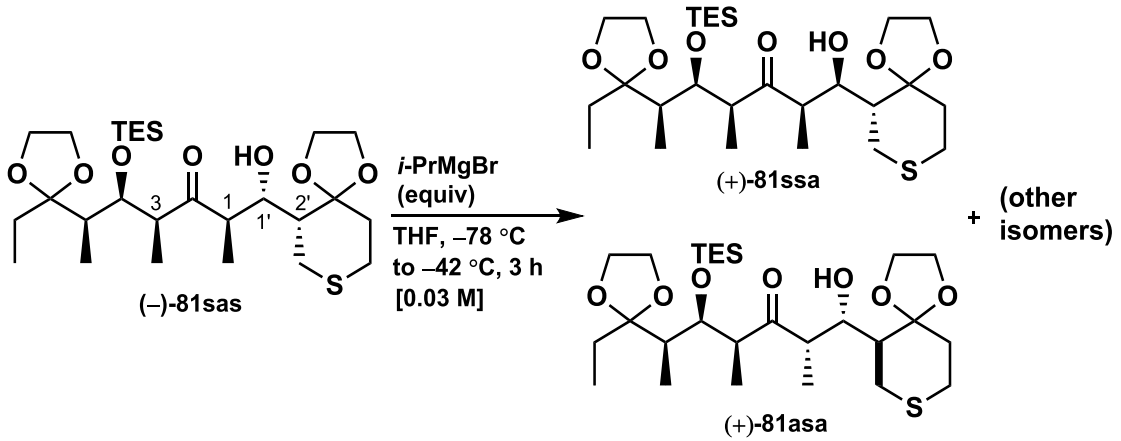
[a]Mole percent determined from ^{1}H NMR of the crude reaction mixture after normalization. [b]Represents the sum of other isomers detected (**81ass**, **81sss** and **81aaa**). [c]Byproducts contain **62b** and OTES elimination products. [d]Not detected.

Attempts were made to improve the conversion at lower temperature by varying the concentration of the reaction (Table 2.32). Increasing or decreasing the reaction concentration

afforded only minimal changes in the product distribution. Thus, 0.034 M concentration was used for further optimization study.

While the Mg(II) aldolates and(or) the Grignard reagents may form aggregates[155-156] at lower temperatures, another possible reason for lower conversion is incomplete deprotonation of the starting aldol (**(−)-81sas**). Consequently, the amount of *i*-PrMgBr was varied from 1.0 to 2.0 equiv (Table 2.33). The results obtained from varying the amount of Grignard reagent were quite unusual — conversion decreased as the amount of *i*-PrMgBr was increased.

Table 2.33. Variation in amounts of Grignard reagents in isomerization of Mg(II) aldolate of **(−)-81sas**.



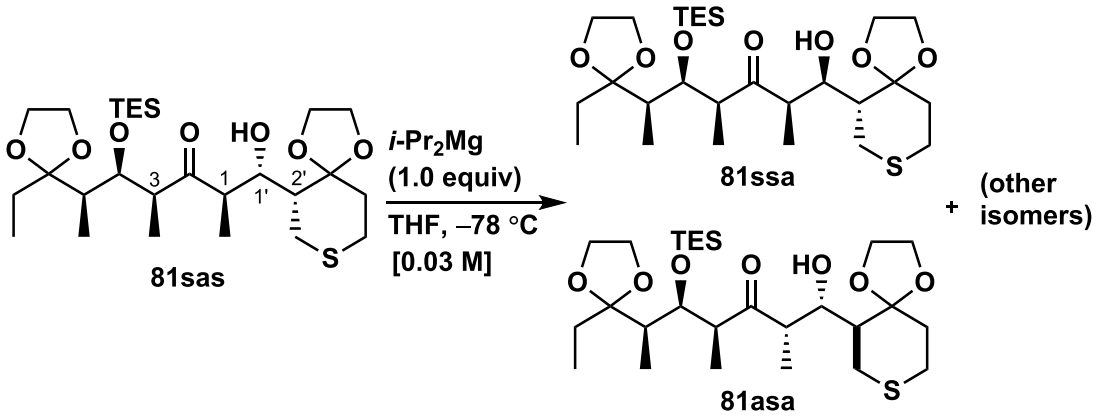
entry	*i*-PrMgBr (equiv)	(−)-81sas[a] (%)	(+)-81ssa[a]: (+)-81asa[a]:Σ[a,b] (%)	byproducts[a,c] (%)
1	1.0	45	27:4:24	ND[d]
2	1.5	64	15:1:15	5
3	2.0	82	2:0:11	5

[a]Mole percent determined from ^{1}H NMR of the crude reaction mixture after normalization. [b]Represents the sum of other isomers detected (**81ass**, **81sss** and **81aaa**). [c]Byproducts contain **40** and OTES elimination products. [d]Not detected.

Grignard reagents exist in equilibrium with dialkyl-Mg and $MgBr_2$ at a lower temperature according to the Schlenk equilibrium (eq 1).[157] If the relative amount of *i*-Pr_2Mg increases at lower temperatures, then it is more likely to be the active species for deprotonation.[158-

[159] To test this hypothesis, *i*-Pr_2Mg was prepared from *i*-PrMgBr according the procedures reported by Cowan and Mosher[159] and Whitesides *et al*.[157] After addition of dioxane to the stock solution of *i*-PrMgBr, the mixture was centrifuged to remove $MgBr_2$-dioxanate as a white solid. The clear top layer was used as a *i*-Pr_2Mg solution whose concentration was assumed to be half the concentration of the starting *i*-PrMgBr solution.

Table 2.34. Variation of temperature and time in reaction of **81sas** with *i*-Pr_2Mg.

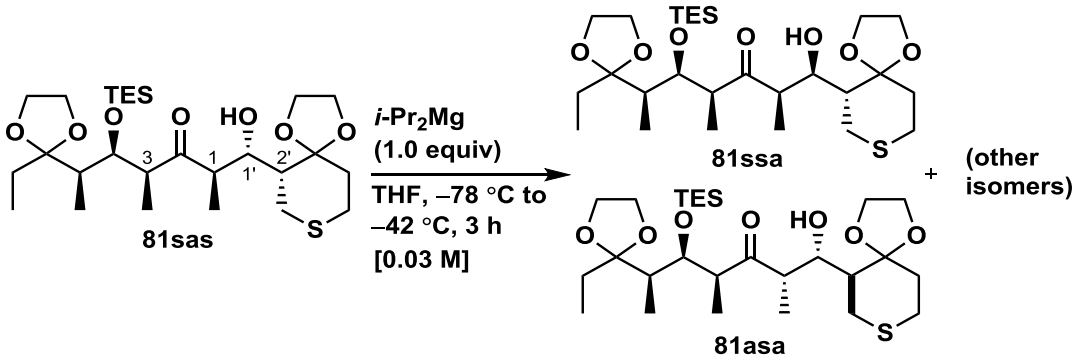


entry	conditions	81sas[a] (%)	81ssa[a]:81asa[a]:Σ[a,b] (%)	byproducts[a,c] (%)
1	−78 °C, 3 h	>90	ND[d]	<10
2	−42 °C, 0.25 h	49	6:10:29	6
3	−42 °C, 0.75 h	29	16:24:24	3
4	−42 °C, 1.5 h	12	22:38:18	10
5	−42 °C, 3 h	11	29:42:12	6
6	−42 °C, 6 h	11	29:42:10	8

[a]Mole percent determined from ^{1}H NMR of the crude reaction mixture after normalization. [b]Represents the sum of other isomers detected (**81ass**, **81sss** and **81aaa**). [c]Byproducts contain **62b** and OTES elimination products. [d]Not determined.

For convenience, racemic **81sas** instead of **(−)-81sas** was used. Initially, **81sas** was treated with 1.0 equiv of *i*-Pr_2Mg at −78 °C. After 3 h, no isomerization products were detected (entry 1, Table 2.34). When the temperature was increased to −42 °C, 51% of the starting material (**81sas**) was consumed within 0.25 h (entry 2). To improve the conversion, the reaction time was increased (entries 3-6). Relatively short increases in reaction times increased the conversion significantly (entries 3 and 4). Further increases in reaction time had a negligible effect on the conversion with moderate changes in product distribution (entries 5 and 6). The conversion could not be increased beyond 89% at a lower temperature (−42 °C).

Table 2.35. Resubjection of crude materials to *i*-Pr_2Mg.



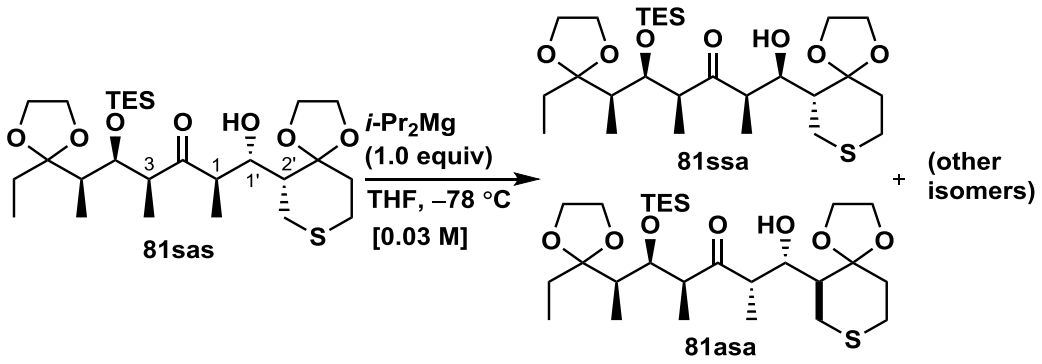
entry	cycle	81sas[a] (%)	81ssa:81asa:Σ[a,b] (%)	byproducts[a,c] (%)	isolated yield[d]
1	1st	11	29:42:12	6	ND[e]
2	2nd	6	25:49:10	10	ND[e]
2[f]	1st	6	25:48:13	7	62%

[a]Mole percent determined from ^{1}H NMR of the crude reaction mixture after normalization. [b]Represents the sum of other isomers detected (**81ass**, **81sss** and **81aaa**). [c]Byproducts contain **62b** and OTES elimination products. [d]Isolated yield of a 1.2:1 mixture of **81asa** and **81ssa**. [e]Not determined. [f]Reaction was performed on 100 mg scale.

To find out whether the ratio of products obtained at −42 °C after 3 h is the equilibrium ratio, the mixture was resubjected to the same reaction conditions (Table 2.35). Minimal changes in product distribution were observed after resubjection, which suggests that equilibrium has been achieved.

In an attempt to increase the conversion, the temperature was increased (Table 2.36). Higher temperatures afforded good conversions with reduced diastereoselectivities. To compare results, **81sas** was treated with *i*-Pr_2Mg under the reaction conditions identical with the reaction of **81sas** with *i*-PrMgBr (see entry 2, Table 2.27). Mainly decomposition products (i.e., ketone **62b** and aldehyde **29a**) were detected along with a small amount (<20%) of isomerized aldol adducts (entry 3).

Table 2.36. Isomerization at higher temperature with *i*-Pr_2Mg.



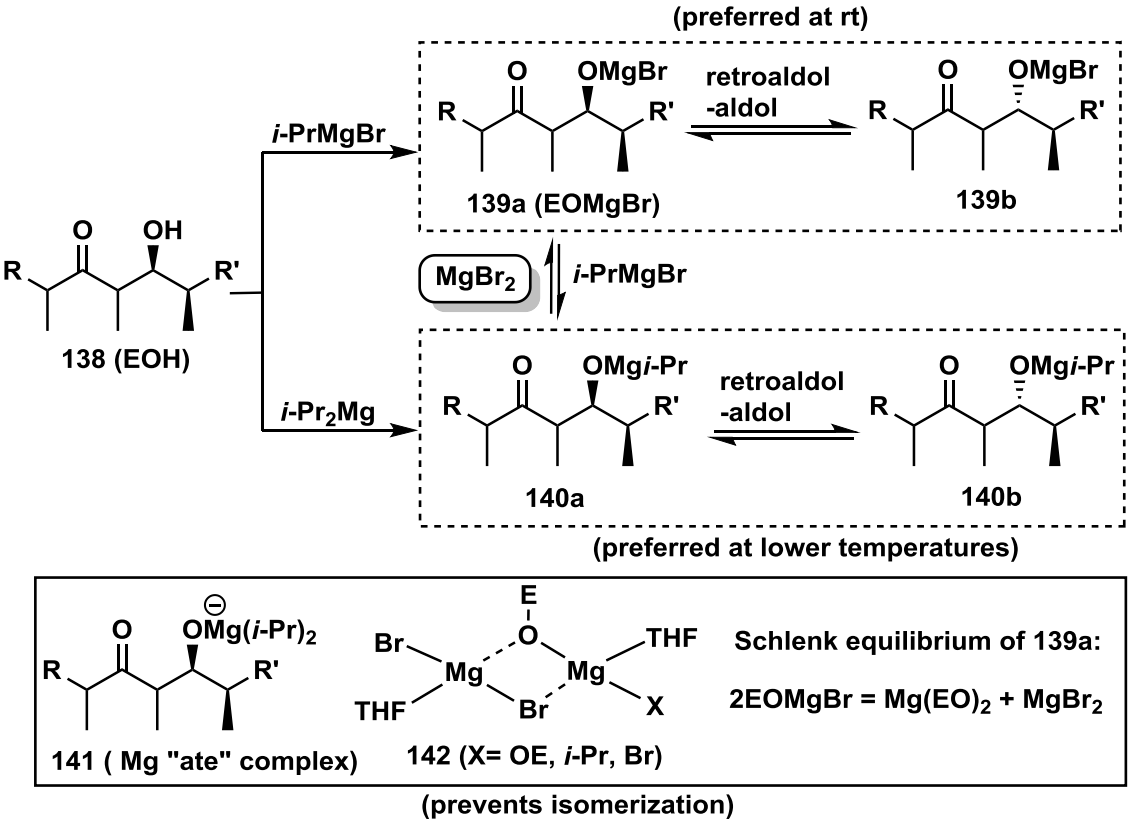
entry	conditions	81sas[a] (%)	81ssa[a]:81asa[a]:Σ[a,b] (%)	byproducts[a,c] (%)
1	−20 °C, 3 h	15	15:34:23	13
2	0 °C, 0.5 h	17	18:17:17	31
3	rt, 72 h	3	9:8:0	80

[a]Mole percent determined from ^{1}H NMR of the crude reaction mixture after normalization. [b]Represents the sum of other isomers detected (**81ass**, **81sss** and **81aaa**). [c]Byproducts contain **62b** and OTES elimination products.

Isomerization at lower temperatures suggests that the species resulting from the reaction of **81sas** with *i*-PrMgBr isomerizes slowly at low temperature (e.g., −42 °C) but undergoes smooth isomerization at room temperature. Conversely, the species resulting from the reaction of **81sas** with *i*-Pr_2Mg is unstable at room temperature but undergoes fast isomerization at low temperature (e.g., −42 °C). This suggests the active species resulting from reactions of **81sas** with *i*-PrMgBr and *i*-Pr_2Mg are not same.

The following pathways are proposed (Scheme 2.27) to qualitatively explain the results obtained from retroaldol-aldol isomerization using *i*-Pr_2Mg and *i*-PrMgBr. Deprotonation of **138** with *i*-PrMgBr at −78 °C forms BrMg-aldolate **139a**. It is possible that the rate of isomerization of **139a** is extremely slow at low temperatures (e.g., −78 °C or −42 °C). Thus, instead of isomerization, **139a** undergoes a displacement reaction with unreacted *i*-PrMgBr, forming aldolate **140a**. Presumably, **140a** is the active species which undergoes isomerization at low temperature. In these cases, conversion is limited to ~50% because only 1 equiv of *i*-PrMgBr is being used.

Scheme 2.27. Proposed pathways for isomerization at different temperatures.

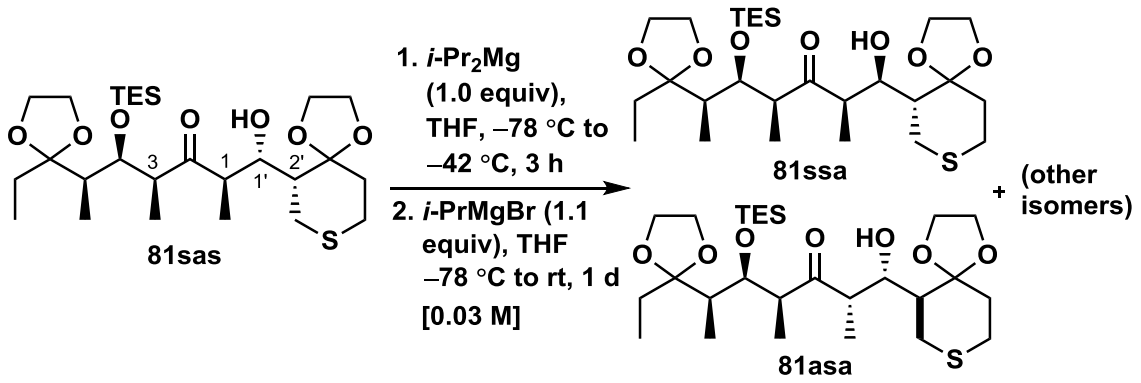


No significant change in conversion was observed when the reaction time was increased at a fixed temperature (see Tables 2.30 and 2.34). It is possible that aldolates like **139a, 140a** or the corresponding diastereomers slowly undergo aggregation, forming **142**, which could lower the reactivity. An increase in temperature may disrupt this aggregate or its formation, resulting higher conversion.

The decrease in conversion with increasing amounts of *i*-PrMgBr can also be explained by the above proposal. For example, addition of excess *i*-PrMgBr can trigger the formation of species like magnesium "ate" complex (**141**) or aggregates (**142**) or dialkoxy-Mg species ($(EO)_2Mg$) via Schlenk equilibria (Scheme 2.27). The rate of isomerization of these species is either extremely slow or they are inactive towards isomerization, causing lower conversion.

Isomerization of Mg(II) aldolates generated with *i*-PrMgBr undergo smooth isomerization at room temperature to afford desired 1′,2′-*anti* (non-Felkin) aldols but no significant isomerization was observed at lower temperatures. In contrast, the isomerization of Mg(II) aldolates generated with *i*-Pr_2Mg underwent isomerization at lower temperature to afford 1′,2′-*anti* (non-Felkin) aldols but decomposition was observed when the reaction was performed at the room temperature. These observations imply that the species causing isomerization at room temperature is not the same as the species which was causing isomerization at lower temperature. Consequently, it is proposed BrMg-aldolate **139a** is the active species that undergoes isomerization at room temperature, whereas *i*-PrMg-aldolate **140a** is the active species that isomerizes at low temperature. It is possible that **140a** is more reactive than **139a**, leading to decomposition at room temperature (see entry 3, Table 2.36). In an ideal situation, the product distribution obtained at low temperature from the reaction of an aldol (e.g., **81sas**) with *i*-PrMgBr should be identical with that obtained with *i*-Pr_2Mg. The differences observed in the product distribution from the reaction of *i*-PrMgBr and *i*-Pr_2Mg are presumably due to the presence of $MgBr_2$ in former case which was absent in the latter.

Table 2.37. Combined method for retroaldol-aldol isomerization.

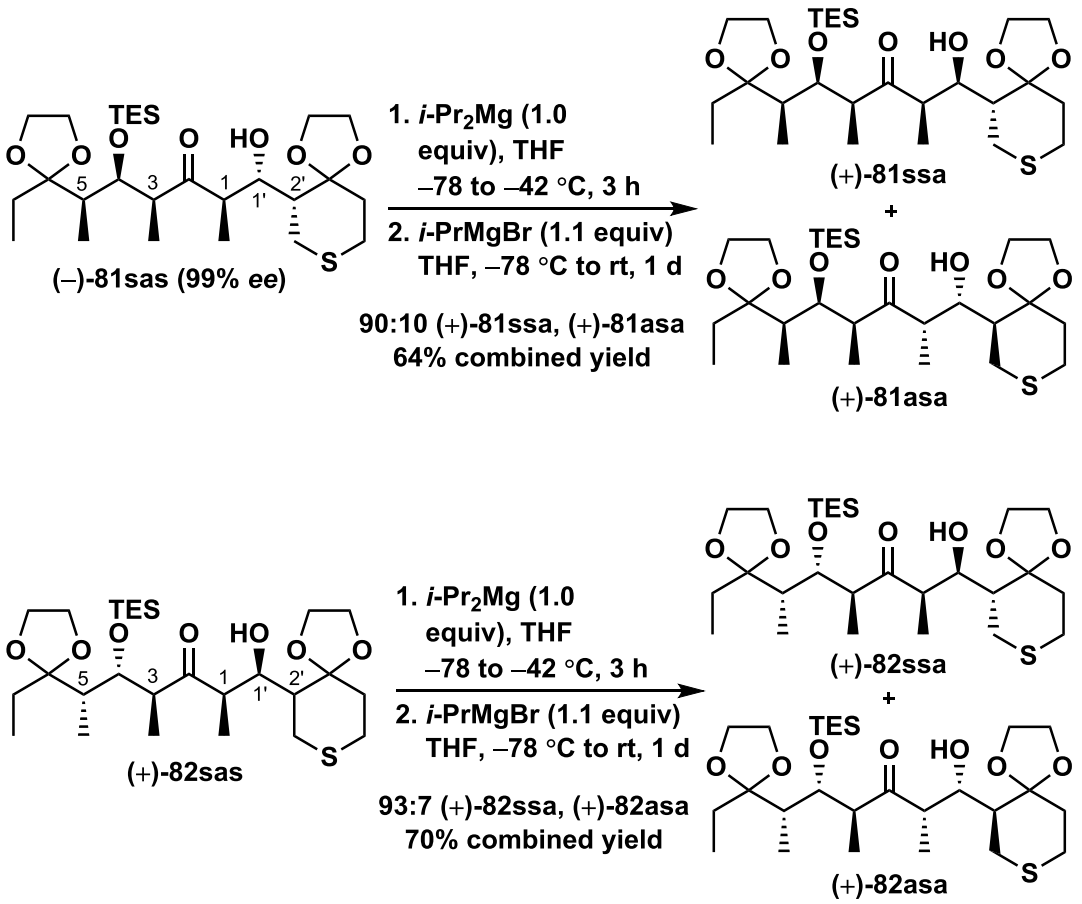


entry	step	81sas[a] (%)	81ssa:81asa:Σ[a,b] (%)	byproducts[a,c] (%)
1	1	11	21:42:16	10
2	2	5	29:49:5	12

[a]Mole percent determined from ^{1}H NMR of the crude reaction mixture after normalization. [b]Represents the sum of other isomers detected (**81ass**, **81sss** and **81aaa**). [c]Byproducts contain **62b** and OTES elimination products. [d]Not detected.

Retroaldol-aldol isomerization was faster with *i*-Pr_2Mg at −42 °C but the amount of desired 1′,2′-*anti* (non-Felkin) aldols was inferior to that obtained using *i*-PrMgBr. On the other hand, the isomerization was slower with *i*-PrMgBr but provided greater amount of 1′,2′-*anti* (non-Felkin) aldols. To have a faster rate and increased amount of 1′,2′-*anti* (non-Felkin) aldols in isomerization of Mg(II) aldolates, both methods were combined and used for isomerization. This combined method provided promising results and significantly decreased the reaction time (Table 2.37). Following this success, enantioenriched aldol adducts were used for further investigation.

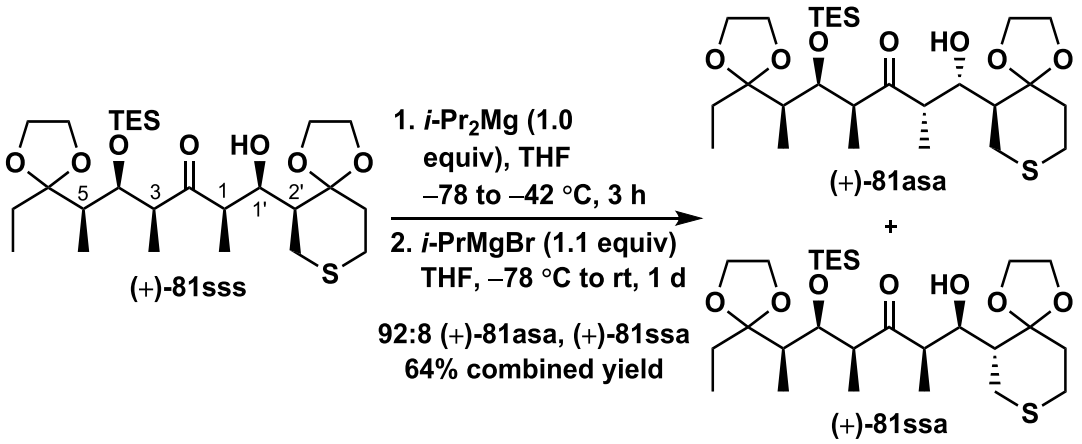
Scheme 2.28. Alternate access to (+)-**81ssa** and **(+)-82ssa** using the combined method.



Isomerization of (−)-**81sas** using the combined method provided 90:10 mixture of **(+)-81ssa** and **(+)-81asa** in 64% combined isolated yield. Although the ratio of **(+)-81ssa** and **(+)-81asa** was slightly improved (from 86:14 to 90:10) using the combined method, the isolated yield was diminished (from 72% to 64%). When **(+)-82sas** was subjected to the combined method, a 93:7 mixture of **(+)-82ssa** and **(+)-82asa** was isolated in 70% combined yield. These results are comparable to the results previously obtained with *i*-PrMgBr.

Isomerization of **(+)-81sss** using the combined method provided a 92:8 mixture of **(+)-81asa** and **(+)-81ssa** in 64% combined isolated yield (Scheme 2.29). Comparing these results with that previously obtained from isomerization of **(+)-81sss** with *i*-PrMgBr (Table 2.29), it can be concluded that the combined method provides a lower yield and lower ratio of **(+)-81asa** and **(+)-81ssa**.

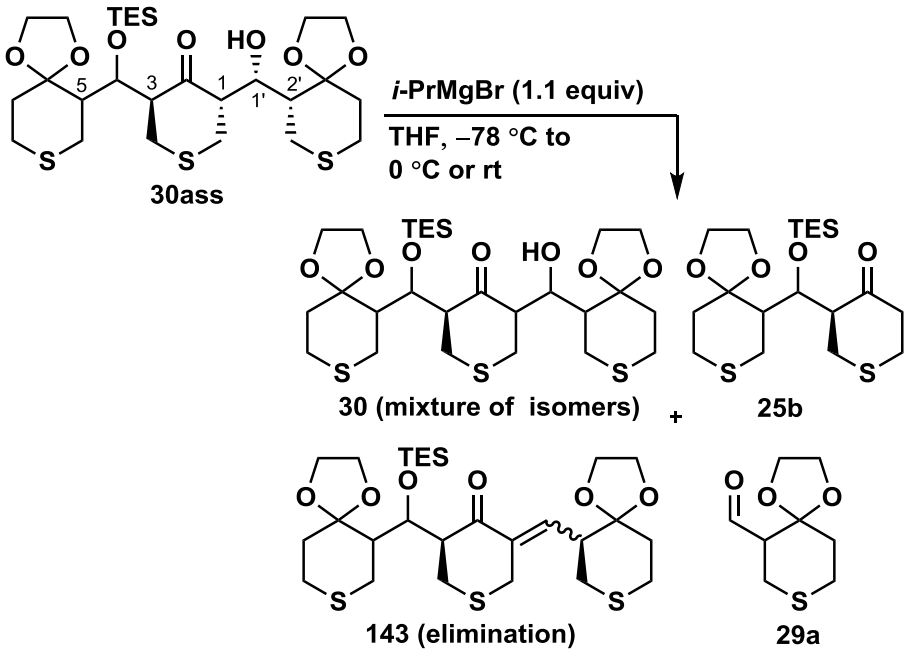
Scheme 2.29. Alternate access to **(+)-81asa** using combine method.



2.3.4.9. Isomerization of Mg(II) aldolates of thiopyranone aldols

The results shown in Tables 2.28 and 2.29 prompted consideration for further study with aldol adducts **30** (Scheme 2.30) derived from thiopyran ketones. Initial attempts at isomerization under the previously optimized conditions were unsuccessful. Isomerization under these conditions provided a mixture of isomers and large amounts of side products such as **143**, **25b**, and **29a** (Scheme 2.30), irrespective of the 3,4-4,5-relative configurations of the starting aldols **30ass**. As a result, the equilibration of the corresponding Mg(II) aldolates could not be established under the previously optimized conditions.

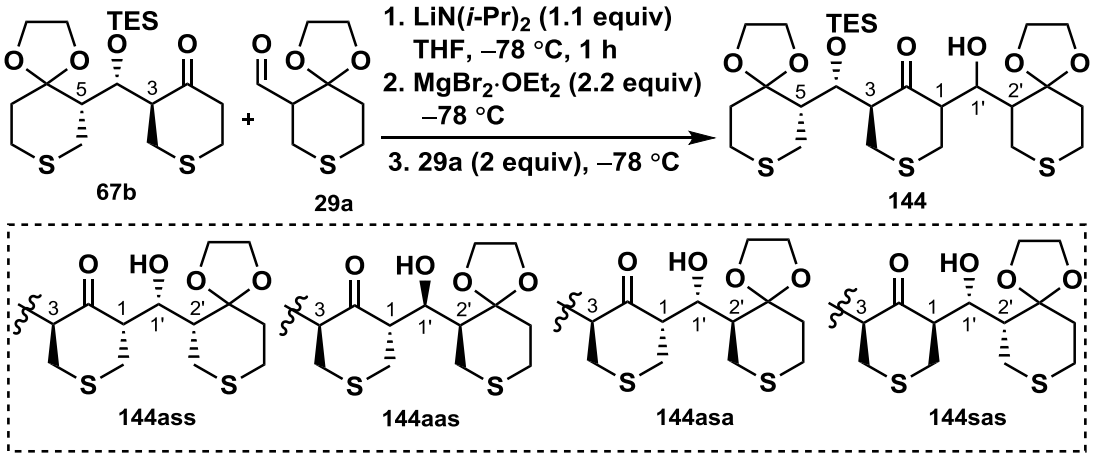
Scheme 2.30. Attempts to generate Mg(II) aldolates of **30ass** with *i*-PrMgBr.



As an alternative, Mg(II) aldolates were generated by transmetallation from corresponding Li aldolates (or enolates).[133] The results of this study are presented below. Ward *et al*. have reported the aldol coupling of the Li enolate of **67b** with **29a** (entry 1, Table 2.38).[84] Adapting the reported[84] procedure, the aldol reaction of the Li enolate of **67b** with **29a** was performed and the aldol reaction time was reduced from 3 h (reported reaction time) to 5 min (entry 2). The modified procedure afforded results comparable to those reported[84] in the literature (compare entries 1 and 2). To determine the kinetic selectivity of the aldol coupling of Mg(II) enolate of **67b** with **29a**, transmetallation[143] of the corresponding Li enolate was performed by reaction with $MgBr_2 \cdot OEt_2$ (step 2) followed by aldol coupling with **29a**. Using commercially available $MgBr_2 \cdot OEt_2$ afforded diastereoselectivity which was identical with that obtained with the corresponding Li enolate, suggesting no transmetallation under the conditions. In contrast, aldol couplings using $MgBr_2 \cdot OEt_2$ that was prepared by adapting the reported procedures[160-161] and stored in a RB flask under argon atmosphere, afforded diastereoselectivities that were different from those obtained from the aldol coupling of the corresponding Li enolate (compare entries 1 and 2 with entries 3-5). The aldol coupling of Li enolate of **67b** with **29a** provided **144sas** as the predominant product whereas similar aldol coupling of the corresponding Mg(II) enolate afforded **144aas** as the major product. Aldol couplings of the Mg(II) enolate of **67b** provided lower

conversions than those obtained from the corresponding Li enolate. No significant change in diastereoselectivity was observed when either the transmetallation time or the aldol reaction time was increased (compare entries 3-5).

Table 2.38. Kinetic selectivity of Mg(II) enolate of **67b**.

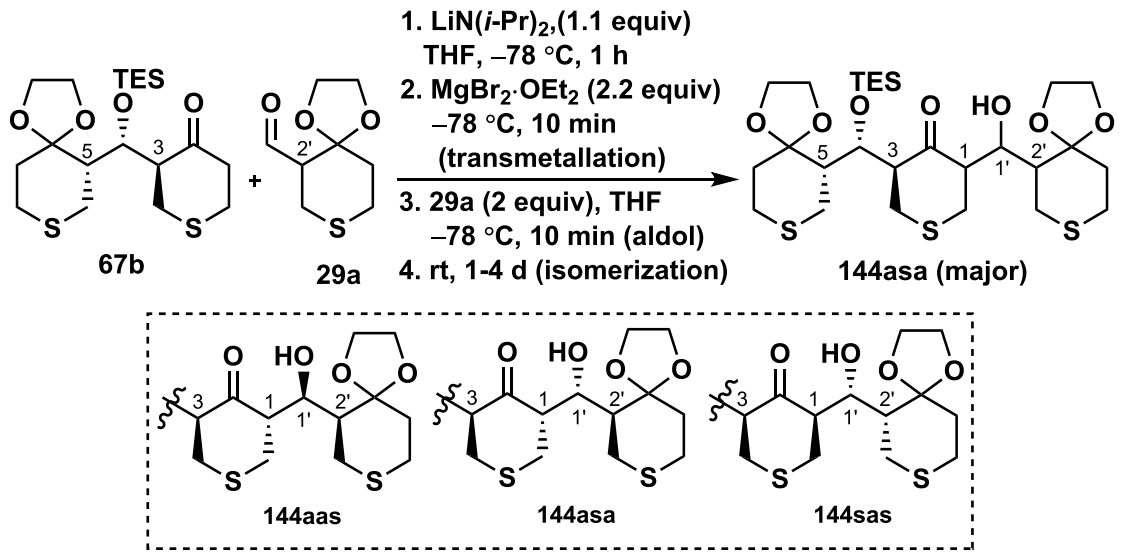


entry	transmetallation time	aldol time	convn[a,b] (%)	(144ass:144aas: 144asa:144sas)[a]	isolated yield[c]
1[g]	-	3 h	>95	4:3:ND[f]:93	89[e]
2[d]	-	5 min	>95	2:6: ND[f]:92	ND[f]
3	10 min	5 min	66	ND[f]:56:33:11	69%
4	30 min	5 min	65	ND[f]:58:30:12	ND[f]
5	10 min	30 min	70	ND[f]:57:31:12	ND[f]

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of the sum of aldol diastereomers and the starting ketone. [c]Isolated yield of the mixture of diastereomers. [d]Represents a Li aldol reaction. [e]Isolated yield of **14sas** diastereomer. [f]Not determined. [g]Reported by Ward *et al*. (see reference 86).

Having suitable conditions for generating Mg(II) aldolates of **67b** in hand, the next goal was to investigate the isomerization (equilibration) of these Mg(II) aldolates under thermodynamic control. To identify suitable conditions for isomerization, the reaction mixture resulting from the aldol coupling of Mg(II) enolate of **67b** with **29a** at −78 °C was warmed to room temperature and monitored by ^{1}H NMR (Table 2.39).

Table 2.39. Optimization of reaction conditions for isomerization.



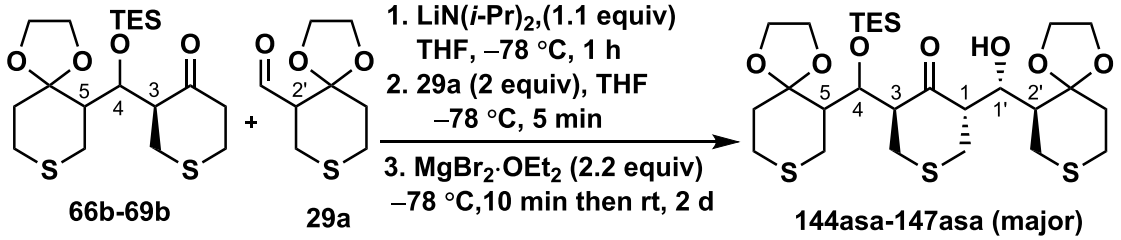
entry	reaction sequence	isomerization time	convn[a,b] (%)	(144asa:144aas :144sas)[a]	isolated yield[c]
1	transmetallation then aldol	1 d	86	70:10:6	ND[d]
2	aldol then transmetallation	1 d	82	69:9:4	ND[d]
3	aldol then transmetallation	2 d	81	73:7:1	76%
4	aldol then transmetallation	4 d	79	70:8:1	ND[d]

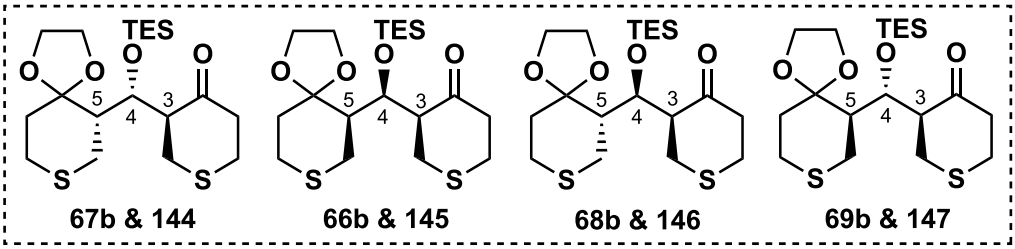
[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of the sum of aldol diastereomers and the starting ketone. [c]Isolated yields of the major diastereomer. [d]Not determined.

No significant byproducts were detected under these conditions. No change in the product distribution was observed when either the order of addition was changed (compare entries 1 and 2, Table 2.39) or the reaction time was increased (compare entries 2 with entries 3 and 4). In all cases, three diastereomers were detected by ^{1}H NMR of the crude reaction mixtures. Diastereomer **144asa** was obtained as the major product along with **144aas** and **144sas**. Among

these three diastereomers, **144asa** had the desired 1′,2′-*anti* relative configuration and was isolated in 76% yield.

Table 2.40. Isomerization of Mg(II) aldolates of **66b-69b** and **29a**.





entry	ketone	convn[a,b] (%)	products	ratio of products[a,c] (%)	isolated yield[d]
1	**67b**	81	**144asa**, **144aas**, **144sas**	73:6:2	76%
2	**66b**	88	**145asa**, **145ass**, **145aas**	(56:11:9)[e]	55%
3	**68b**	70	**146asa**, **146sas**, **146aas**	41:13:9	38%
4	**69b**	>95	**147asa**	>95:5	79%

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Estimated from the ratio of the sum of aldol diastereomers and the starting ketone. [c]No significant change in the ratio of products was observed when parallel reactions were conducted for extended time (4 d). [d]Isolated yields of the major diastereomer. [e]Plus 12% of other diastereomers.

Each of the four possible diastereomers of ketone (**67b-69b**) were subjected to the above aldol/isomerization conditions (Table 2.40). High conversions were obtained for all four ketones. The 1,3-*anti*-1,1′-*syn*-1′,2′-*anti* (**asa**) diastereomer was formed as the major product. The relative configurations of the ketones had a strong influence on the ratios of the products; excellent diastereoselectivities were obtained in isomerizations of Mg(II) aldolates of 3,4-*anti* ketones (**67b** and **69b**), while isomerizations of Mg(II) aldolates of 3,4-*syn* ketones (**66b** and **68b**) provided

moderate diastereoselectivities. Only one of the four possible 1′,2′-*anti* (non-Felkin) aldols was present in all cases.

2.3.5. Structure determination of 1′,2′-*anti* (non-Felkin) aldols

The 1′,2′-*anti* (non-Felkin) aldol adducts shown in Figure 2.12 were obtained from the isomerization of Mg(II) aldolates of the corresponding 1′,2′-*syn* (Felkin) aldols. The structures of **144asa**-**147asa** were known from the work of Theaker, N.[134] All the possible diastereomers of **125**,[106, 133] **126**,[53] and **127**[85-86] (except **127aaa**) (Table 2.25) have previously been reported in the literature and were easily identified in the ^{1}H NMR spectra of the isomerization mixtures (e.g., the signals for HC-1′ were particularly diagnostic).

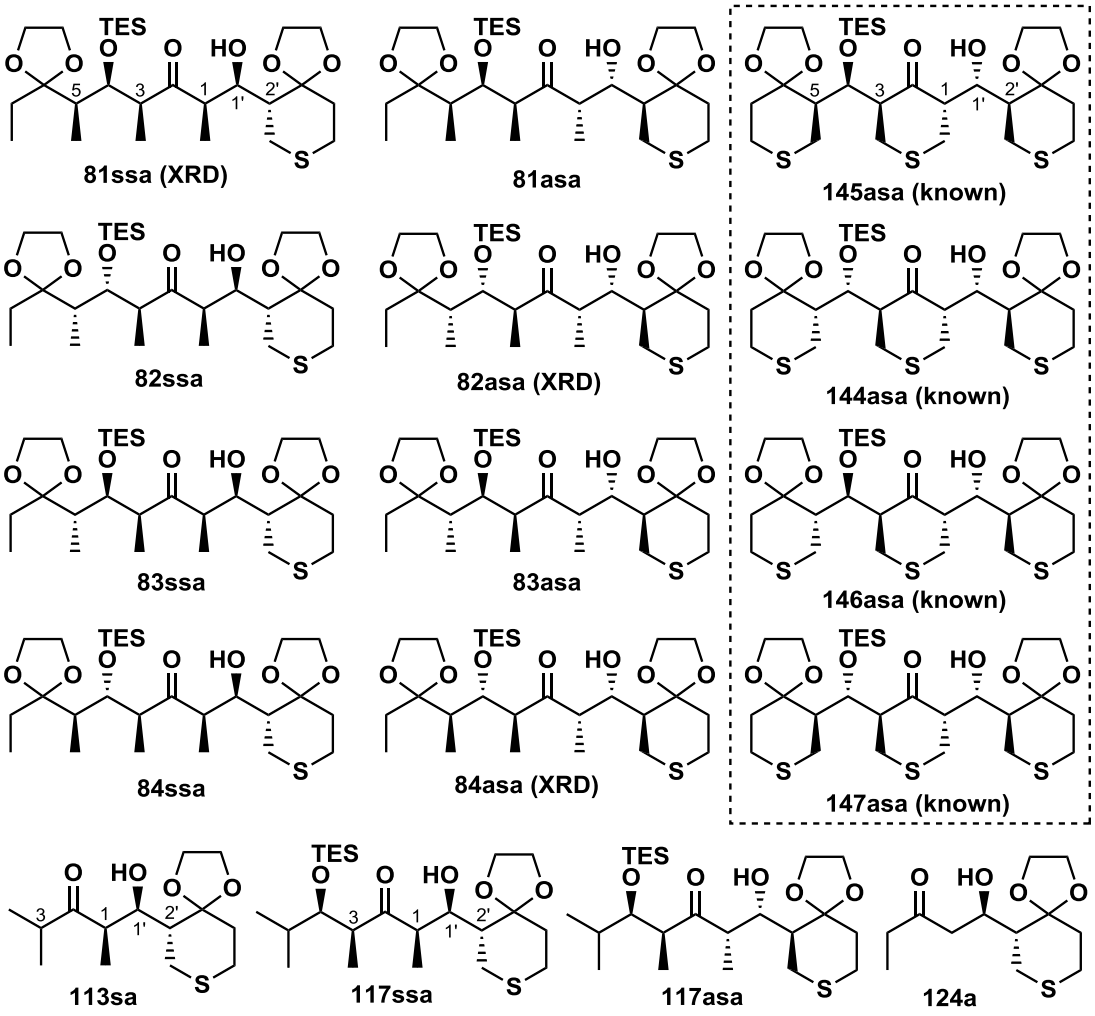
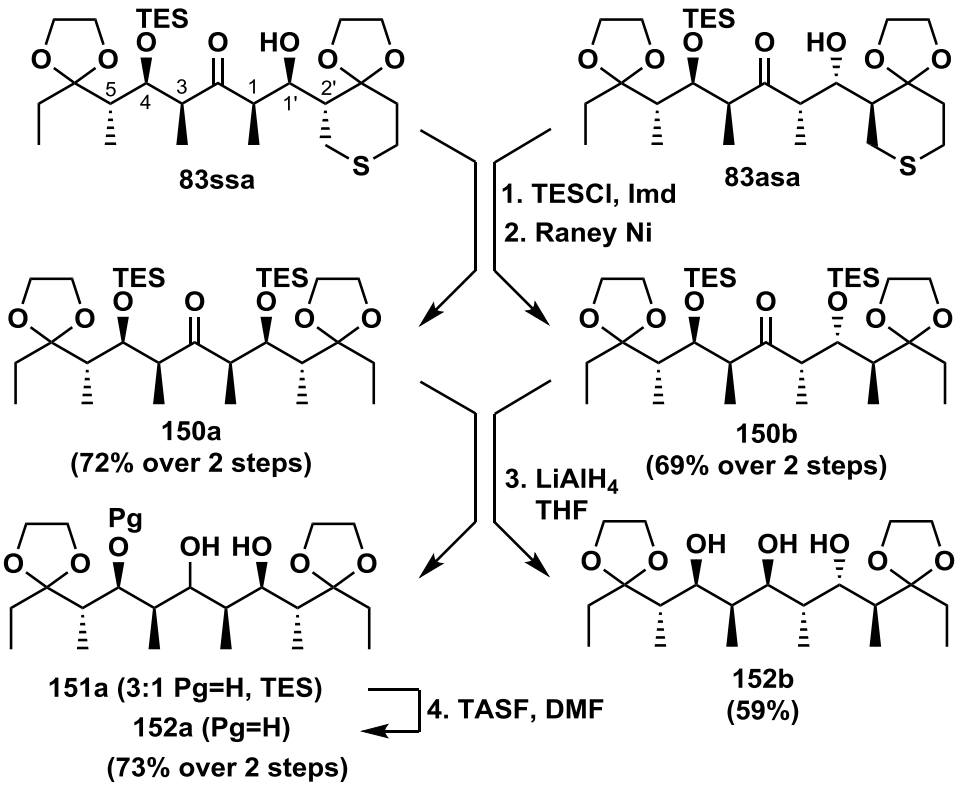


Figure 2.12. The 1′,2′-*anti* (non-Felkin) aldols obtained from the isomerization study.

To establish the structures of 1′,2′-*anti* (non-Felkin) aldols shown in Figure 2.12, the ^{1}H and ^{13}C NMR data for each of these aldol adducts were carefully analyzed and correlated to the corresponding 3-pentanone aldol adducts **61**. The structures of all four possible diastereomers of **61** were previously established (see section 2.2.1.1.). Comparison of the ^{1}H and ^{13}C NMR data (chemical shifts and coupling constants) for **81ssa**-**84ssa**, **81asa**-**84asa**, **113sa**, **117ssa**, and **117asa** with that of **61** allowed the direct assignments of 1,1′-*syn*-1′,2′-*anti* (sa) relative configurations. However, the 1,3-relative configurations of **81ssa**-**84ssa**, **81asa**-**84asa**, **117ssa**, and **117asa** could not be established from the above NMR correlations. It was assumed that the 3,4- and 4,5-relative configurations of the starting ketones are retained in the corresponding isomerized products because isomerization of each the aldol adducts of four possible ketones provided the corresponding **ssa** and **asa** aldol adducts. Therefore, establishing the 1,3-1,1′-1′,2′-relative configurations of **81ssa**-**84ssa** and **81asa**-**84asa** will secure the overall structure. Structural analysis of **83ssa** and **83asa** showed both can lead to symmetric compounds after simple two step modifications. To take advantage of the symmetry elements, each of these aldols **83ssa** and **83asa** were subjected to TESCl (Et_3SiCl) and imidazole (Imd) (Scheme 2.31). Desulfurization of the resulting TES-protected derivatives provided **150a** and **150b**. Indeed, both compounds were symmetric as evident by their ^{1}H and ^{13}C NMR spectra — the number of proton signals was half that expected for an asymmetric diastereomer and a reduced number of carbon signals (13 instead of 33) was observed. To be symmetric, **150a** must have 1,1′-*syn*-1′,2′-*anti* (sa) relative configuration because the starting ketone has a 3,4-*syn*-4,5-*anti* (sa) relative configuration.

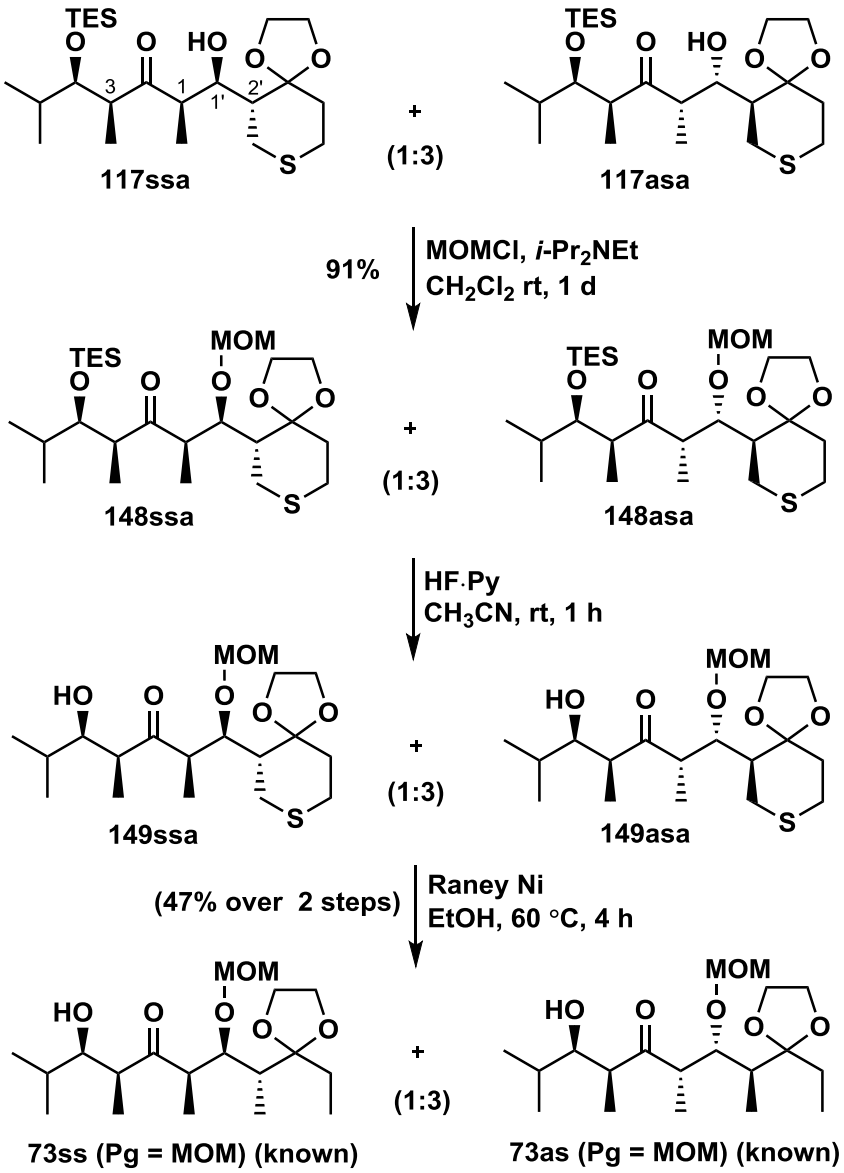
Scheme 2.31. Structure determination of **83ssa** and **83asa**.



Among **150a** and **150b** (Scheme 2.31), one has 1,3-*syn* and the other one has 1,3-*anti* relative configurations. To find out the 1,3-relative configuration, each product was reduced with $LiAH_4$ in THF. The diastereomer with 1,3-*syn* relative configuration would be symmetric after reduction whereas the diastereomer with 1,3-*anti* relative configuration would not be symmetric after reduction. Reduction of **150a** provided a 3:1 mixture of mono-TES protected aldol **151a** and a triol **152a** which was converted to a single isomer of triol **152a** after TES-deprotection with TASF. Reduction of **150b** cleanly provided triol **152b** as a single isomer. The ^{1}H and ^{13}C NMR spectra of **152a** showed the number of signals expected for a symmetric compound suggesting **152a** has a plane of symmetry (i.e., sigma symmetric). This is possible only if **152a** has a 1,3-*syn* relative configuration, thus establishing the ,3-*syn*-1,1′-*syn*-1′,2′-*anti* (ssa) relative configurations of the starting aldol **83ssa**. In contrast, the ^{1}H and ^{13}C NMR spectra of **152b** showed the number of signals expected for an asymmetric compound, thus establishing the 1,3-*anti* relative configuration for **152b** and the 1,3-*anti*-1,1′-*syn*-1′,2′-*anti* (asa) relative configurations for **83asa**. The structures of remaining **ssa**/**asa** diastereomeric pairs (i.e., **81ssa/81asa**, **82ssa/82asa**, and **84ssa/84asa**) depicted in Figure 2.12 were secured by X-ray diffraction of crystals obtained for

one of the two possible diastereomers of the pairs (i.e., **81ssa**, **82asa** and **84asa**) (Figures 6.2-6.4 in Appendix). Based on the above structure determinations, **124a** was assumed to have 1′,2′-*anti* relative configuration because it was obtained from the reactions identical to the remaining 1′,2′-*anti* (non-Felkin) aldols depicted in Figure 2.12.

Scheme 2.32. Structure determination of **117ssa** and **117asa**.



To establish the structures of **117ssa** and **117asa**, a 1:3 mixture of these aldols was transformed to the corresponding 1:3 mixture of known aldol adducts **73ss**[124] (Pg = MOM) and **73as**[124] (Pg = MOM) in three steps (Scheme 2.32). Initial protection of the free OH groups of the

1:3 mixture of **117ssa** and **117asa** with MOMCl followed by deprotection of the TES groups with HF·Py provided 1:3 mixture of **149ssa** and **149asa**. Finally, desulfurization of the mixture provided a 1:3 mixture whose ^{1}H and ^{13}C NMR data closely matched those of the known aldol adducts **73ss**[124] (Pg = MOM) and **73as**[124] (Pg = MOM).

3. CONCLUSIONS

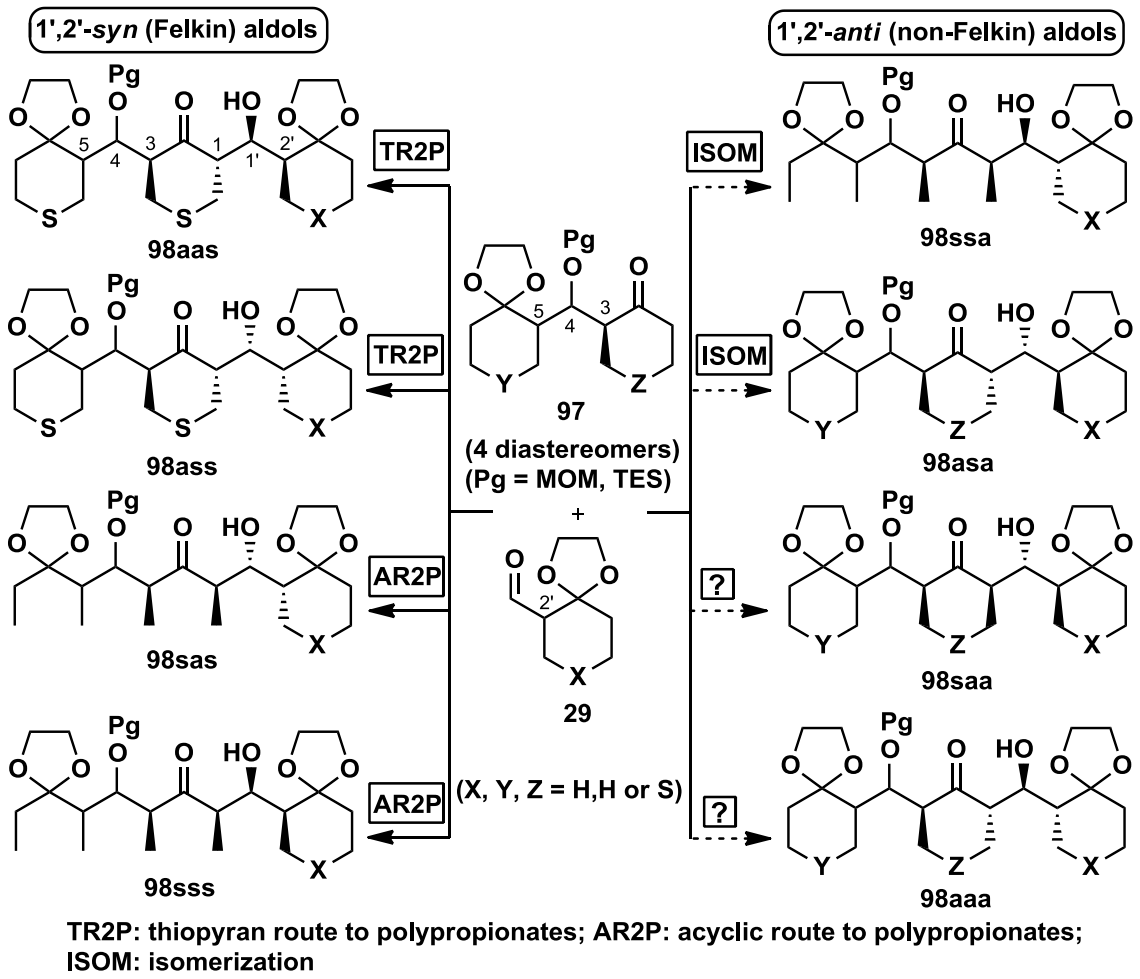


Figure 3.1. Stereochemical diversity in the aldol coupling of **97** and **29**.

Starting from the same ketones and aldehyde, it was possible to selectively obtain six of the eight possible diastereomers in the aldol coupling of **97** and **29** (Figure 3.1). The previously developed thiopyran route to polypropionates (TR2P) provided selective access to two of the eight possible diastereomers **98aas** (X = S) (= **30aas** in Figure 1.12) and **98ass** (X = S) (= **30ass** in Figure 1.12). To have access to other diastereomers of **98**, the diastereoface selectivities of the ketones were reversed from 1,3-*anti* to 1,3-*syn* by using the acyclic ketones **96** (Y = Z = H,H) (= **26** in Figures 1.12 and 1.14). This newly developed methodology (acyclic route to polypropionates or AR2P) provided selective access to the remaining two 1′,2′-*syn* (Felkin) aldols **98sas** (X = H,H; S) (= **31sas** in Figures 1.12 and 1.14) and **98sss** (X = H,H, S) (= **31sss** in Figures 1.12 and 1.14).

The 1,1′-relative configuration (i.e., relative topicity) was of controlled by the proper choice of the enolate type (B or Ti) and(or) enolate geometry (*E* or *Z*). For instance, the (*E*)-enol dicyclohexylborinates provided aldol adducts with 1,1′-*anti* relative configuration whereas the Ti(IV) "ate" (*E*)-enolates (in TR2P) and Ti(IV) (*Z*)-enolates (in AR2P) provided aldol adducts with 1,1′-*syn* relative configurations.

All attempts under kinetically controlled conditions to alter the diastereoface selectivities of enolate additions to chiral aldehydes **29** from 1′,2′-*syn* (Felkin) to 1′,2′-*anti* (non-Felkin) proved futile. Alternatively, thermodynamic equilibration of the Mg(II) aldolates of 1′,2′-*syn* (Felkin) aldols provided selective access to two of the four possible 1′,2′-*anti* (non-Felkin) aldols (Scheme 2.24); i.e., **98ssa** (X = S) (= **31ssa** in Figures 1.12 and 1.14) and **98asa** (X = S)(= **31ssa** in Figures 1.12 and 1.14). Now, it is possible to access 75% of the possible aldol diastereomers (24/32) for the aldol coupling illustrated in Figure 3.1 without significant modification of the coupling reactants. Therefore, it can be concluded from the above study that, in principle, it should be possible to access all the eight possible diastereomers by having proper control of all three stereocontrol elements. Each of these aldol diastereomers were synthesized in enantiomerically enriched form using non-racemic ketones. Thus, these aldol diastereomers are useful in polypropionate syntheses.

To best of my knowledge, there are no direct methods available in the literature to access diastereomers **98saa** and **98aaa** via aldol coupling of **97** and **29** (Figure 3.1). Judging from the results summarized in Scheme 2.13, one can expect that a $MgBr_2 \cdot OEt_2$ promoted Mukaiyama aldol reaction between **29a** (X = S) and trimethylsilyl enol ethers of **97** (Y = Z = H,H) might provide access to these 1′,2′-*anti* (non-Felkin) aldols. All efforts toward this goal were jeopardized because of the decomposition of the TMS-enol ethers of **97** (Y = Z = H,H) to the corresponding ketones in the presence of $MgBr_2 \cdot OEt_2$ (Scheme 2.14). Attempted Mukaiyama aldol couplings of TMS-enol ethers of **97** (Y = Z = H,H) with **29a** (X = S) in the presence of $TiCl_3(O\textit{i}\text{-Pr})$ also failed to produce 1′,2′-*anti* (non-Felkin) aldols (Scheme 2.11). Further investigation is required to promote the Mukaiyama aldol couplings of **97** with **29** in the presence of $MgBr_2 \cdot OEt_2$ or $TiCl_n(O\textit{i}\text{-Pr})_{4-n}$ (n = 1-3) or other Lewis acids.

4. EXPERIMENTAL

4.1. General methods

Anhydrous solvents were distilled under argon atmosphere prior to the use as follows. THF from benzophenone sodium ketyl, CH_2Cl_2 from CaH_2, MeOH from $Mg(OMe)_2$, DMSO from CaH_2 under reduced pressure, DMF over P_2O_5 and stored over 4 Å molecular sieves. Dioxane was degassed with a constant flow of argon and stored over 4 Å molecular sieves for several days prior to use. All experiments involving air- and(or) moisture sensitive compounds were conducted in an oven dried round-bottom flask or vial capped with a rubber septum and attached via needle and connecting tubing to a mercury bubbler under argon atmosphere. Low temperature baths were toluene/liquid N_2 (-95 °C), acetone/CO_2(s) (−78 °C), acetonitrile/CO_2(s) (−42 °C), and ice/water (0 °C). Unless otherwise noted, the reaction temperatures refer to the temperature of the cooling bath. Thin layer chromatography (TLC) was carried out on a glass plates (1 × 3 cm) pre-coated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and(or) aqueous phosphomolybdic acid (PMA) solution [PMA (40 g), $Ce(SO_4)_2$ (10 g), and H_2SO_4 (50 mL) and diluted to 1 L with water], or with basic KMnO4 [$KMnO_4$ (3 g), and Na_2CO_3 (3 g), diluted with 200 mL water] followed by charring on a hot plate. Preparative TLC (PTLC) was carried out on glass plates (20 × 20 cm) pre-coated (0.25 mm) with silica gel 60 F_{254}. A 1 cm vertical strip removed from the plate and was visualized by the same techniques as described for TLC. Flash column chromatography (FCC) was performed according to Still *et al*.[162] with Merck silica gel 60 (40-63 mm). All mixed solvents eluents are reported as v/v solutions. Unless otherwise mentioned, all reported compounds were homogenous by TLC and by ^{1}H NMR spectroscopy. Concentration of samples refers to removal of volatiles with a rotary evaporator under vacuum generated by a water aspirator. Further evacuation at ca. 0.1 torr with a vacuum pump generally followed rotary evaporation.

4.2. Spectral data

High resolution mass spectra (HRMS) were obtained on a VG 70E double focusing high resolution spectrometer. Electron impact (IE) ionization was accomplished at 70 eV, chemical ionization (CI) at 50 eV with ammonia as the reagent gas. Alternatively, HRMS was obtained on a LC-MS/MS time-of-flight high resolution spectrometer with electrospray ionization (ESI) from

methanol solution. Infrared (IR) spectra were recorded on a Bio-Rad Fourier transform interferometer using a diffuse reflectance cell (DRIFT) or using a KBr disc; only diagnostic peaks and(or) intense peaks are reported. NMR solvent $CDCl_3$ was passed through small plug of basic alumina prior to use. NMR spectra were measured in $CDCl_3$ solution at an operating frequency of 500 MHz or 600 MHz for ^1H and 125 MHz or 150 MHz for ^{13}C, respectively. The signal due to the solvent ($CDCl_3$ for ^{13}C NMR) or residual protonated solvent ($CHCl_3$ for ^1H NMR) served as the internal standard: $CDCl_3$ (7.26 δ_H, 77.23 δ_C); C_6D_6 (7.16 δ_H, 128.39 δ_C). The ^1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the followings: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of coupling constants (*J*) corresponds to the order of the multiplicity assignment. Coupling constants are reported to the nearest 0.5 Hz. The NMR assignments were made on the basis of chemical shifts (δ)[117] and coupling constants (*J*)[42, 116] and were confirmed (where necessary) by homonuclear decoupling,[163] gCOSY,[164] gHSQC,[165-166] gHMBC,[165, 167] and NOE.[168-169] The multiplicity of ^{13}C NMR signals refers to the number of H′s attached (i.e., s = C, d = CH, t = CH_2, q = CH_3) and was determined by gHSQC. Specific rotations ($[\alpha]_D$) are the average of 6-8 determinations. The measurements were performed at ambient temperature on a Rudolph DigiPol 781 instrument using a 1 mL, 10 dm cell; the units are 10^{-1} deg cm^2 g^{-1} and the concentration (*c*) are reported in g/100 mL. The values reported are rounded to reflect the accuracy of the measured concentrations (the major source of error). HPLC analyses were carried out using an Agilent Technologies 1200 series liquid chromatograph.

4.3. Materials

The following compounds and reagents were prepared as described previously: **29a**;[102] **29b**;[124] **30**;[84] **57**;[124] **59** (M = $SiMe_3$);[124] **60**;[124] **62**;[124] **(+)-62b**;[109] **63**;[124] **(+)-63b**;[119] **64**;[124] (−)-**64b**;[84, 124] **65**;[124] (−)-**65b**;[84, 124] **66**;[84] **67**;[84] **68**;[84] **69**;[84] **89**;[108] (−)-**89sa**;[122] (−)-**89aa**;[122] **102a**;[53] **105**,[90] **106**;[108] **111**;[142] **112**;[142] **125**;[106, 133] **126**;[53] **127**;[85-86] IBX;[170] W-2 Raney nickel;[171] MOM-Cl;[172] (*c*-Hex)$_2$BCl.[173]Commercially available *n*-BuLi and *t*-BuLi were routinely titrated with diphenyl acetic acid as the titrant and indicator. Et_3N, *i*-Pr_2NEt, *i*-Pr_2NH, and $(Me_3Si)_2NH$ were distilled from CaH_2 under argon and stored over KOH. $TiCl_4$ was distilled from CaH_2 under argon prior to use. Ti(O*i*-Pr)$_4$ was distilled under reduced pressure and stored in a Schlenk flask under argon. Solutions of TiCl(O*i*-Pr)$_3$ and $TiCl_2$(O*i*-Pr)$_2$ (ca. 1.7 M in THF) were freshly prepared according

to procedure reported by Urpi´ *et al*.[136] All other reagents were commercially available and, unless otherwise mentioned, were used as received.

4.4. Experimental procedures and characterization data

General procedure for desulfurization.

A suspension of Raney nickel (W2; ca. 0.3 mL settled volume per 0.1 mmol of substrate) in EtOH (ca. 8 mL per mL of Raney Ni) was added to the substrate and the mixture was heated under reflux with vigorous stirring. The reaction was monitored by TLC and when the substrate was no longer detected (0.5–4 h depending on the substrate and Raney Ni activity), the mixture was decanted and the solid was resuspended in EtOH (5 mL) and heated under reflux with vigorous stirring for 10 min. This washing procedure was repeated with ethyl acetate, and acetone. The combined organic layers were filtered through Celite® and concentrated to give the crude product.

General procedure for the preparation of MOM ethers.

i-Pr_2EtN (3.5 equiv) and MOM-Cl (3 equiv) were added to a stirred solution of alcohol (0.4-0.8 M in CH_2Cl_2) at 0 °C. The mixture was allowed to warm to ambient temperature and reaction progress was monitored by TLC. When the reaction was complete, the mixture was diluted with saturated aq NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated to give the crude product.

General procedure for the preparation of Et_3Si ethers.

Imidazole (2.3 equiv) and Et_3SiCl (2 equiv) were sequentially added to a stirred solution of alcohol (0.4-0.8 M in DMF) at room temperature. Reaction progress was monitored by TLC and when the reaction was complete, the mixture was diluted with ethyl acetate and washed sequentially with saturated aq NH_4Cl and brine, dried over Na_2SO_4, and concentrated to give the crude product.

Preparation of $MgBr_2 \cdot OEt_2$.

Adapting the procedures reported by Rowley[160-161] and Schreiber[160-161], commercially available magnesium metal was activated by sequential washing with 10% HCl, water (×3), acetone (×2), diethyl ether (×2) and then dried under vacuum. The activated Mg metal (6.9 g, 0.28

mol) was added to a three-neck round bottom flask fitted with thermometer and condenser followed by addition of anhydrous Et_2O (100 mL) under argon atmosphere. The flask was cooled to below 15 °C (temperature inside the flask) using an ice-bath and then dibromoethane (20.0 mL, 0.23 mol) was carefully added dropwise over 1.5 h (CAUTION! exothermic reaction). The temperature was maintained below 15 °C throughout the addition. After the addition, the ice-bath was removed and the reaction mixture was warmed to room temperature over 30 min. When the boiling of ether stopped, the mixture was allowed to stand for 15 min and then carefully decanted into a clean round bottom flask under argon leaving the unreacted Mg behind. Then the round bottom flask was submerged into an ice-bath to crystallize the $MgBr_2 \cdot OEt_2$. After 30 min, the supernatant was decanted and the solid was dried under vacuum. The grayish white solid $MgBr_2 \cdot OEt_2$ (49.1 g, 67%) was stored under argon and used as required.

Preparation of *i*-PrMgBr Grignard Reagent.

According to the general procedure reported by Knochel *et al.*[174], dry THF (19 mL) was added to a 100 mL flask placed in a water bath containing magnesium turnings (388 mg, 15.98 mmol) under argon atmosphere. A solution of DIBAL-H (0.1 mL, 1.0 M in cyclohexane) was added to the stirred solution. After 5 min, *i*-PrBr (1.0 mL, 1.31 g, 10.60 mmol) was and allowed to stirred at room temperature (maintained using a water bath). After 3 h, the solution was allowed to stand at room temperature for 1 h without any stirring to settle down the unreacted fine magnesium. Finally, the clear solution was transferred to a Schlenk flask using cannula leaving black colored fine magnesium in the original flask and stored under argon. The stock solution was titrated against salicylaldehyde phenylhydrazone in THF at room temperature according to the procedure reported by Love et al.[175] The strength of the solution was found to be 0.4 M.

General Procedure for Retroaldol-Aldol Isomerization with *i*-PrMgBr.

i-PrMgBr (0.40 M in THF, 1.1 equiv) was added dropwise via syringe over 30 s to a stirring solution of **aldol** (0.05-0.2 mmol, 1 equiv; 0.3 M in THF) in a Schlenk tube at –78 °C under argon. After 15 min, the cooling bath was removed and the mixture allowed to warm to ambient temperature. After 30 min, the rubber septum was replaced with glass stopper (thereby sealing the reaction vessel) and reaction mixture was stirred at room temperature for 3-6 days. The mixture was cooled in an ice bath and the reaction was quenched by addition of phosphate buffer (pH 7;

2-4 mL) with vigorous stirring. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to obtain the crude product that was analyzed by ^1H NMR and then fractionated.

General procedure for preparation of Li (*Z*)-enolates and their aldol reactions (Table 2.10).

A solution of LiHMDS (0.6−0.8 M) was prepared by addition of n-BuLi (1.5−3 M in hexanes; 1.1 equiv) to a stirred solution of $(Me3Si)_2NH$ (1.2 equiv) in THF (ca. 1 M) at 0 °C under argon. An aliquot of the above solution (1.1 equiv of LiHMDS) was added via syringe to a stirring solution of ketone (ca. 0.1−0.2 M in THF; ca. 30− 100 mg, 0.1−0.3 mmol, 1 equiv) at −42 °C under argon. After 1.5-2 h, the solution was cooled to −78 °C and thiopyran aldehyde (1.5 equiv) dissolved in THF (0.6-0.8 M) was added via syringe. After 5 min, the reaction was quenched by addition of saturated aq NH_4Cl, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with satd. $NaHSO_3$ solution (only for the reactions of TES ketones) and dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR and then fractionated.

General procedure for aldol reactions via the (*E*)-enol borinate (Tables 2.7-2.8, 2.13).

Preparation of the enolate. Conditions A: $(c\text{-Hex})_2BCl$ (ca. 2 M in hexanes; 1.5-2.5 equiv) and Et_3N [1.2 equiv with respect to $(c\text{-Hex})_2BCl$] were sequentially added to a stirring solution of ketone (1 equiv) in Et_2O (ca. 0.15-0.20 M) at the indicated temperature under Ar. Conditions B: The lithium enolate of the ketone (1 equiv) was prepared as described in the general procedure for aldol reactions of Li (*Z*)-enolate. The reaction mixture was cooled to −78 °C and $(c\text{-Hex})_2BCl$ (ca. 2 M in hexanes; 1.6-2.2 equiv) was added. After 15 min, the reaction vessel was transferred to a −42 °C bath and stirred for 2 h.* Aldol reaction. After the indicated enolization time, the reaction mixture was cooled to –78 °C (if necessary) and a solution of the aldehyde was added via syringe. After 2-3 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath and after vigorous stirring

*This procedure produces the (*E*)-enol borinate with high stereoselectivity (>19:1).[121]

for 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR and then fractionated.

General procedure for aldol reactions via the (*Z*)-enol borinate (Table 2.9).

Et_3N (1.2 equiv with respect to 9-BBN-OTf) and 9-BBN-OTf (0.5 M in hexanes; 1.5−1.6 equiv) were sequentially added via syringe to a stirred solution of ketone (ca. 30−60 mg, 0.1−0.17 mmol, 1 equiv) in diethyl ether (ca. 0.08−0.17 M) at −78 °C under argon. After the indicated enolization time, a solution of aldehyde (3 equiv) in diethyl ether (0.3-1.0 M) was added via syringe. After 3−4 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 10 mL/mmol of boron), MeOH (10 mL/mmol of boron), and 30% aq H_2O_2 (5 mL/mmol of boron) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^1H NMR and then fractionated.

General procedure for aldol reactions via the Ti(IV) (*Z*)-enolate (Tables 2.11-2.12, 2.14).

After preparation of the lithium (*Z*)-enolate at −42 °C as described above, a solution of $Ti(O\textit{i}\text{-}Pr)_4$ or $TiCl_n(O\textit{i}\text{-}Pr)_{4-n}$ (n = 1, 2)[137] (ca. 1.7 M in THF; 2.2 equiv) was added via syringe and stirring continued at that temperature for 1 h. Formation of a red color (for $TiCl_2(O\textit{i}\text{-}Pr)_2$) or a bright greenish yellow color (for $TiCl(O\textit{i}\text{-}Pr)_3$) was observed and persisted throughout the transmetallation time. The mixture was cooled to −78 °C and a solution of the aldehyde (3 equiv) in THF (0.6-0.8 M) was added via syringe (the color was changed to yellow within 1-2 min of aldehyde addition).The intensity of the yellow color diminished over time and became light yellow after 16 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (6 mL) and extracted with ethyl acetate. The combined organic layers were washed with satd. $NaHSO_3$ solution and passed through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and concentrated. to give the crude product that was analyzed by ^1H NMR and then fractionated.

General procedure for reactions of α-bromoketones (Tables 2.19-2.21, Scheme 2.16).

In a Schlenk flask, commercially available $MgBr_2 \cdot OEt_2$ (1 equiv) was added to a stirring solution of aldehyde (1 equiv, 0.08 M) and bromoketone (1.5 equiv) in THF (ca. 0.08 M) at room temperature under argon followed by addition of activated Mg metal* (20 equiv). The flask was sealed with glass stopper and the heterogeneous mixture was warmed to 40 °C using an oil bath. After the indicated reaction time, the reaction mixture was cooled to 0 °C and quenched by addition of phosphate buffer (pH 7, 7 mL) and then allowed to warm to room temperature with vigorous stirring. Finally, the mixture was diluted with H_2O and extracted with CH_2Cl_2 (×2). The combined organic layers were dried over Na_2SO_4 and concentrated to obtain crude product which was analyzed by ^1H NMR and then fractionated.

General Procedure for isomerizations with *i*-PrMgBr.

i-PrMgBr (0.4 M in THF, 1.1 equiv) was added dropwise over 30 sec. via syringe to a stirring solution of aldol (50-70 mg, 0.09-0.13 mmol, 1 equiv)) in THF (0.03 M) at −78 ℃ in a Schlenk tube under Ar atmosphere. After 15 min, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 30 min, the rubber septum was replaced with glass stopper and the sealed vessel was stired at room temperature for 3-6 days. The reaction mixture was cooled to 0 ℃ and quenched by addition of phosphate buffer (pH 7, 2-4 mL) and then allowed to warm to room temperature with vigorous stirring. Finally, the mixture was diluted with H_2O and extracted with CH_2Cl_2 (×2). The combined organic layers were dried over Na_2SO_4 and concentrated to obtain crude product which was analyzed by ^1H NMR and then fractionated.

General procedure for isomerizations with *i*-Pr_2Mg (Tables 2.30-2.37, Schemes 2.28-2.29).

Preparation of *i*-Pr_2Mg solution: Adapting procedures reported by Cowan and Mosher[159] and Whiteside *et al*.,[157] to a solution of *i*-PrMgBr (0.4 M in THF, 1.0 equiv) in a small test tube under argon was added dioxane (1.0 equiv) dropwise at room temperature and white precipitate was formed. The precipitate was removed from resulting slurry by

* Commercially available magnesium metal was activated by sequential washing with 10% HCl, water (×3), acetone (×2), diethyl ether (×2) and then dried under vacuum. The activated magnesium was stored in a bottle and used as required.

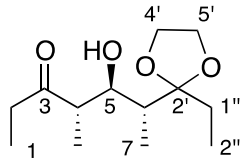
centrifugation. The supernatant was used as *i*-Pr_2Mg solution and the concentration was assumed to be half that of the initial solution (i.e., 0.2 M). Reaction of **(−)-81sas** with *i*-Pr_2Mg: To a stirring solution of **(−)-81sas** in THF (0.03 M) at −78 °C under argon was added dropwise *i*-Pr_2Mg solution (0.2 M, 1.0 equiv). After 10 min, the reaction mixture was warmed to the indicated temperature. After the indicated reaction time, the mixture was quenched and extracted according to the general procedure reported for isomerization with *i*-PrMgBr. The crude product was analyzed by ^1H NMR and then fractionated by FCC.

General procedure for isomerizations with *i*-Pr_2Mg and then with *i*-PrMgBr (Schemes 2.28-2.29).

Reaction with *i*-Pr_2Mg. A freshly prepared solution of *i*-Pr_2Mg (0.2 M in THF) was added via syringe to a stirring solution of aldol (ca. 20−25 mg, 0.04−0.05 mmol, 1 equiv) in THF (ca. 0.03 M) at −78 °C under argon. After 10 min, the solution was warmed to −42 °C. After 3 h, the reaction was quenched by addition of phosphate buffer (pH 7, 1-2 mL) at 0 °C and then warmed to room temperature with vigorous stirring. Finally, the mixture was diluted with H_2O and extracted with CH_2Cl_2 (×2). The combined organic layers were dried over Na_2SO_4, concentrated to obtain the crude product. Reaction with *i*-PrMgBr. The crude product obtained from the reaction with *i*-Pr_2Mg was azeotropically dried with benzene and then transferred to a Schlenk tube using THF (ca. 0.03 M) under argon. The stirring reaction mixture was cooled to −78 °C and a solution of *i*-PrMgBr (0.4 M in THF) was added dropwise via syringe. After 15 min, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 30 min, the rubber septum was replaced with glass stopper and the sealed vessel was allowed to stir at room temperature for 1 d. The mixture cooled to 0 °C and quenched by addition of phosphate buffer (pH 7, 1-2 mL) and then warmed to room temperature with vigorous stirring. Finally, the mixture was diluted with H_2O and extracted with CH_2Cl_2 (×2). The combined organic layers were dried over Na_2SO_4, concentrated to obtain crude product which was analyzed by ^1H NMR and then fractionated by PTLC.

General procedure for isomerizations of Mg(II) aldolates of thiopyranone aldols (Table 2.40).

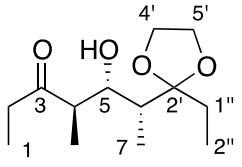
The Li enolates were prepared by adapting the procedure reported by Ward *et al*.[84] A solution of freshly prepared LDA (0.17 M in THF; 1.1 equiv) was added via syringe to a stirring solution of thiopyran ketones (20 mg, 0.047 mmol, 1 equiv)) in THF (0.1 M) at −78 °C in a Schlenk tube under Ar. After 1 h, a solution of aldehyde **29a** (18 mg, 0.09 mmol, 2 equiv) in THF (0.48 M) was added via syringe. After 5 min, synthesized solid $MgBr_2 \cdot OEt_2$ (2.2 equiv) was added at −78 °C. After 10 min, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 30 min, the rubber septum was replaced with glass stopper and the sealed vessel was allowed to stir at room temperature for 2 days. The mixture was cooled to 0 °C and quenched by addition of phosphate buffer (pH 7, 2-4 mL) and then allowed to warm to room temperature with vigorous stirring. Finally, the mixture was diluted with H_2O and extracted with CH_2Cl_2 (×2). The combined organic layers were dried over Na_2SO_4 and concentrated to obtain crude product that was analyzed by ^1H NMR and then fractionated.



(60aa)

(4*S*,5*R*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-hydroxy-4-methylheptan-3-one (60aa).

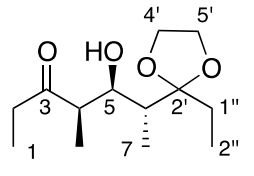
The crude product obtained by desulfurization of **61aa** (50 mg, 0.18 mmol) according to the general procedure was fractionated by PTLC (40% ethyl acetate in hexanes) to give the title compound (43 mg, 97%) whose NMR data were consistent with those previously reported.[124]



(60as)

(4*R*,5*S*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-hydroxy-4-methylheptan-3-one (60as).

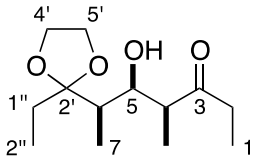
The crude product obtained by desulfurization of **61as** (46 mg, 0.17 mmol) according to the general procedure was fractionated by PTLC (40% ethyl acetate in hexanes) to give the title compound (40 mg, 98%) whose NMR data were consistent with those previously reported.[124]



(60sa)

(4*R*,5*R*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-hydroxy-4-methylheptan-3-one((60sa).

The crude product obtained by desulfurization of a 14:1 mixture of **61ss** and **61sa**, respectively (25 mg, 0.09 mmol), according to the general procedure was fractionated by PTLC (40% ethyl acetate in hexanes) to give the title compound as a 14:1 mixture of **60ss** and **60sa**, respectively (21 mg, 94%). The NMR data of the major compound were consistent with those previously reported.[124]



(60ss)

(4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-hydroxy-4-methylheptan-3-one (60ss).[124]

From aldol. $BF_3{\cdot}OEt_2$ (1.7 mL, 1.9 g, 13 mmol) was added dropwise via syringe over 5 min to a stirring solution of **29b** (2.08 g, 13.2 mmol) and **59** (M = TMS) (4.16 g, 26.4 mmol) in CH_2Cl_2 (200 mL) at –78 °C under argon. After 1.5 h, the reaction was quenched by addition of saturated aq NH_4Cl (10 mL) and, after warming to ambient temperature, the mixture was extracted with CH2Cl2. The combined organic layers were dried over Na_2SO_4 and concentrated to obtain the crude product whose ^1H NMR indicated the presence of a 10:1 mixture of **60ss** and **60as**, respectively. Fractionation of the crude by FCC (30% ethyl acetate in hexanes) gave a 2.5:1 mixture of **60ss** and **60as**, respectively (343 mg, 11%), and the title compound (2.03 g, 63%). From **61ss**. The crude product obtained by desulfurization of **61ss** (53 mg, 0.19 mmol) according to the general procedure was fractionated by FCC (30% ethyl acetate in hexanes) to give the title compound (46 mg, 97%) whose NMR data were consistent with those previously reported.[124]

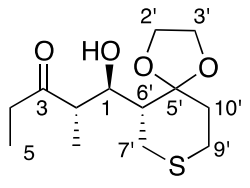
colorless oil, TLC R_f = 0.4 (35% ethyl acetate in hexanes).

IR (3529, 1708) ν_{max} 3529, 1708 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (1H, d, *J* = 9 Hz, HC-5), 4.03-3.92 (4H, m, H_2C-4′, H_2C-5′), 3.10 (1H, br s, HO), 2.78 (1H, dq, *J* = 9, 7 Hz, HC-4), 2.54 (1H, dq, *J* = 18, 7 Hz, H_2C-2), 2.41 (1H, dq, *J* = 18, 7 Hz, H_2C-2), 1.81 (1H, dq, *J* = 1, 7 Hz, HC-6), 1.68 (2H, ap q, *J* = 7.5 Hz, H_2C-1″), 1.21 (3H, d, *J* = 7 Hz, H_3CC-4), 1.03 (3H, t, *J* = 7 Hz, H_3C-1), 0.93 (3H, d, *J* = 7 Hz, H_3C-7), 0.86 (3H, t, *J* = 7.5 Hz, H_3C-2″).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.7 (s, C-3), 114.7 (s, C-2′), 71.6 (d, C-5), 65.7 (t, C-4′), 65.0 (t, C-5′), 50.2 (d, C-4), 39.9 (d, C-6), 35.6 (t, C-2), 28.1 (t, C-1″), 14.9 (q, CH_3C-4), 8.2 (q, C-2″), 7.8 (q, C-1), 7.4 (q, C-7).

HRMS *m/z* calcd. for $C_{13}H_{24}O_4$+Na^+ 267.1566, found 267.1567 (ESI).



(61aa)

(1*R*,2*S*)-*rel*-1-Hydroxy-2-methyl-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)pentan-3-one (61aa).

$MgBr_2 \cdot OEt_2$ (1.04 g, 4.03 mmol) was added to a stirred solution of **29a** (250 mg, 1.33 mmol) in CH_2Cl_2 (5.0 mL) at room temperature under argon. After 5 min, the resulting creamy off-white suspension was placed in an ice bath, and after 15 min, a solution of **59** (M = $SiMe_3$) (358 mg, 2.26 mmol) in CH_2Cl_2 (0.7 mL) was added dropwise via syringe. After stirring for 2 h, the reddish pink reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give yellow oil that whose ^{1}H NMR spectrum indicated the presence of a 6.5:1 mixture of **61aa** and **61sa**, respectively. Fractionation of the crude product by FCC (50-70% Et_2O in hexanes) gave **61sa** (40 mg, 11%), a 3.2:1 mixture of **61aa** and **61sa**, respectively (14 mg, 4%), and the title compound (250 mg, 67%).

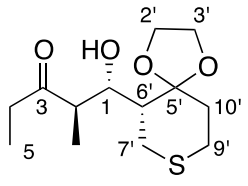
pale yellow viscous oil, TLC R_f = 0.45 (50% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3495, 1698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16-4-10 (2H, m, HO, HC-1), 4.03-3.95 (4H, m, H_2C-2' & H_2C-3'), 2.87 (1H, dd, *J* = 3, 14 Hz, HC-7'), 2.80 (1H, dq, *J* = 4.5, 7 Hz, HC-2), 2.74 (1H, dd, *J* = 7.5, 14 Hz, HC-7'), 2.71 (1H, ddd, *J* = 3.5, 8.5, 13.5 Hz, HC-9'), 2.65 (1H, ddd, *J* = 3.5, 7.5, 13.5 Hz, HC-9'), 2.61-2.48 (2H, m, H_2C-4), 2.13 (1H, ddd, *J* = 3, 8.5, 13.5 Hz, HC-10'), 2.01 (1H, ddd, *J* = 3, 7, 7.5 Hz, HC-6'), 1.75 (1H, ddd, *J* = 3.5, 7.5, 13.5 Hz, HC-10'), 1.21 (3H, d, *J* = 7 Hz, H_3CC-2), 0.99 (3H, t, *J* = 7 Hz, H_3C-5).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2 (s, C-3), 110.6 (s, C-5'), 74.6 (d, C-1), 64.7 (t, C-2'), 64.0 (t, C-3'), 49.4 (d, C-2), 46.5 (d, C-6'), 35.3 (t, C-4), 34.7 (t, C-10'), 30.0 (t, C-7'), 26.8 (t, C-9'), 14.2 (q, CH_2C-2), 7.7 (q, C-5).

HRMS *m/z* calcd for $C_{13}H_{22}O_4S$ 274.1239, found 274.1237 (EI).



(61as)

(1*S*,2*R*)-*rel*-1-Hydroxy-2-methyl-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)pentan-3-one (61as).

(c-Hex)$_2$BCl (1.1 M in hexane; 1.0 mL, 1.1 mmol) and Et_3N (0.22 mL, 0.16 g, 1.6 mmol) were sequentially added via syringe to a stirred solution 3-pentanone (0.14 mL, 0.12 g, 1.4 mmol) in dry Et_2O (7.6 mL) at 0 °C under argon. After 1 h, the mixture was cooled to –78 °C and a solution of **29a** (150 mg, 0.80 mmol) in Et_2O (0.4 mL) was added dropwise via syringe. After 16 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 3.0 mL), MeOH (3.0 mL) and 30% aqueous H_2O_2 (1.5 mL) with vigorous stirring. The reaction vessel was transferred into an ice bath and after vigorous stirring for 30 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to obtain the crude product whose ^{1}H NMR indicated the presence of a single

aldol diastereomer (dr >20:1). Fractionation of the crude product by FCC (50% Et_2O in hexanes) afforded the titled compound (185 mg, 85%).

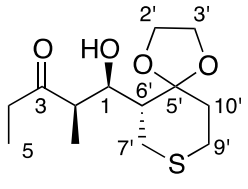
white solid, TLC R_f = 0.45 (50% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3491, 1713 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (1H, ddd, *J* = 2, 2.5, 9 Hz, HC-1), 4.07-3.89 (4H, m, H_2C-2' & H_2C-3'), 3.11 (1H, d, *J* = 2.5 Hz, HO), 3.00 (1H, dd, *J* = 11.5, 14 Hz, HC-7'), 2.80-2.71 (2H, m, HC-2 & HC-9'), 2.61 (1H, ddd, *J* = 2.5, 3, 14 Hz, HC-7'), 2.56-2.47 (3H, m, H_2C-2 & HC-9), 2.09 (1H, ddd, *J* = 3, 4.5, 14 Hz, HC-10'), 1.99 (1H, ddd, *J* = 2, 3, 11.5 Hz, HC-6'), 1.69 (1H, ddd, *J* = 3.5, 12, 14 Hz, HC-10'), 1.01 (3H, t, *J* = 7 Hz, H_3C-5), 0.97 (3H, d, *J* = 7 Hz, H_3CC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4 (s, C-3), 110.2 (s, C-5'), 71.8 (d, C-1), 64.8 (t, C-2'), 64.3 (t, C-3'), 47.9 (d, C-2), 46.3 (d, C-6'), 36.6 (t, C-4), 36.3 (t, C-10'), 26.6 (t, C-9'), 26.0 (t, C-7'), 13.9 (q, CH_2C-2), 7.5 (q, C-5).

HRMS *m/z* calcd for $C_{13}H_{22}O_4S$ 274.1239, found 274.1237 (EI).



(61sa)

(1*R*,2*R*)-*rel*-1-Hydroxy-2-methyl-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-pentan-3-one (61sa).

For preparation via aldol reaction of the TMS enol ether of 3-pentanone with **29a**, see the preparation of **61aa**. Isomerization of **61as** (111 mg, 0.40 mmol) for 6 d according to the general procedure (*i*-PrMgBr) gave a crude product that was a single aldol adduct by ^{1}H NMR. Fractionation of the crude product by FCC (40-50% Et_2O in hexanes) provided the title compound (83 mg, 75%).

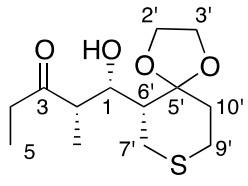
white solid, TLC R_f = 0.45 (50% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3496, 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (1H, br dd, *J* = 2, 8.5 Hz, HC-1), 4.04-3.95 (4H, m, H_2C-2' & H_2C-3'), 3.94 (1H, br s, HO), 2.84 (1H, dd, *J* = 2.5, 14 Hz, HC-7'), 2.77 (1H, ddd, *J* = 3.5, 9, 13.5 Hz, HC-9'), 2.70 (1H, dddd, *J* = 1.5, 4, 7.5, 13.5 Hz, HC-9'), 2.66-2.58 (3H, m, HC-2 & HC-4 & HC-7'), 2.53 (1H, dq, *J* = 17.5, 7.5 Hz, HC-4), 2.19 (1H, ddd, *J* = 4, 9, 13.5 Hz, HC-10'), 1.96 (1H, ddd, *J* = 3, 6, 9 Hz, HC-6'), 1.83 (1H, ddd, *J* = 3.5, 7.5, 13.5 Hz, HC-10'), 1.10 (3H, d, *J* = 7 Hz, H_3CC-2), 1.05 (3H, t, *J* = 7.5 Hz, H_3C-5).

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0 (s, C-3), 110.7 (s, C-5'), 70.9 (d, C-1), 64.9 (t, C-2'), 64.2 (t, C-3'), 48.0 (d, C-2), 46.2 (d, C-6'), 34.5 (t, C-10'), 33.7 (t, C-4), 29.4 (t, C-7'), 26.9 (t, C-9'), 8.14 (q, C-5 or CH_2C-2), 8.10 (q, C-5 or CH_2C-2).

HRMS *m/z* calcd for $C_{13}H_{22}O_4S$ 274.1239, found 274.1233 (EI).



(61ss)

(1*S*,2*S*)-*rel*-1-Hydroxy-2-methyl-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)pentan-3-one (61ss).

From aldol (B (*Z*)-enolate). Et_3N (0.11 mL, 76 mg, 0.75 mmol) and 9-BBN-OTf (0.5 M in hexanes; 1.3 mL, 0.64 mmol) were sequentially added via syringe to a stirred solution of 3-pentanone (74 μL, 60 mg, 0.70 mmol) in Et_2O (3.0 mL) at 0 °C under argon. After 10 min, the reaction vessel was removed from the ice bath and the mixture allowed to warm to ambient temperature. After 1 h, the mixture was cooled to –78 °C and a solution of **29a** (92 mg, 0.58 mmol) in ether (0.9 mL) was added. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL) with vigorous stirring. The reaction vessel was transferred to an ice bath and after vigorous stirring for 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR indicated the presence of a

3.5:1 mixture of **61ss** and **61sa**, respectively. Fractionation of the crude product by FCC (40% ethyl acetate in hexanes) afforded 10.5:1 mixture of **61ss** and **61sa** (62 mg, 85%), respectively, that was further fractionated by PTLC (60% Et_2O in hexanes) to get a 2.3:1 mixture of **61ss** and **61sa** (13 mg, 19%), respectively, and **61ss** (47 mg, 64%; dr >20:1). From aldol (Ti(IV) (*Z*)-enolate). 3-pentanone (52 μL, 42 mg, 0.49 mmol) was added dropwise via syringe to a stirred solution of freshly prepared LiHMDS (0.70 M in THF, 0.50 mL, 0.35 mmol) at –78 °C under Ar. After 1 h, freshly prepared $ClTi(O\textit{i}\text{-}Pr)_3$ (0.55 M in THF, 1.3 mL, 0.71 mmol) was added and the reaction vessel was transferred to a –50 °C. After 2 h, the mixture was cooled to –78 °C and a solution of **29a** (50 mg, 0.32 mmol) in THF (0.8 mL) was added via syringe. After 3 h, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with ethyl acetate. The combined organic layers were filtered through a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and the combined filtrate and ethyl acetate washings were concentrated to give the crude product whose ^1H NMR spectrum indicated the presence of 12:1 mixture of **61ss** and **61as**, respectively. Fractionation of the crude preduct by FCC (40% ethyl acetate in hexanes) gave the title compound as a 12:1 mixture with **61as** (59 mg, 81%).

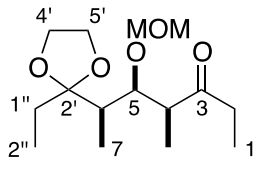
colorless liquid, TLC R_f = 0.41 (50% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3524, 1706 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (1H, ddd, *J* = 1.5, 3, 7.5 Hz, HC-1), 4.07-3.93 (4H, m, H_2C-2' & H_2C-3'), 3.11 (1H, d, *J* = 1.5 Hz, HO), 2.96 (1H, dd, *J* = 10.5, 14 Hz, HC-7'), 2.83 (1H, dq, *J* = 7.5, 7 Hz, HC-2), 2.76 (1H, ddd, *J* = 3, 11.5, 13.5 Hz, HC-9'), 2.72 (1H, br d, *J* = 14 Hz, HC-7'), 2.59-2.48 (2H, m, HC-4, HC-9'), 2.47 (1H, dq, *J* = 18, 7 Hz, HC-4), 2.09 (1H, ddd, *J* = 3, 5.5, 13.5 Hz, HC-10'), 1.87 (1H, ddd, *J* = 3, 3.5, 10.5 Hz, HC-6'), 1.70 (1H, ddd, *J* = 3, 11.5, 14 Hz, HC-10'), 1.19 (3H, d, *J* = 7 Hz, H_3CC-2), 1.04 (3H, t, *J* = 7 Hz, H_3C-5).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9 (s, C-3), 110.0 (s, C-5'), 69.4 (d, C-1), 64.8 (t, C-2'), 64.5 (t, C-3'), 49.7 (d, C-2), 47.3 (d, C-6'), 35.8 (t, C-10'), 35.2 (t, C-4), 26.9 (t, C-7'), 26.7 (t, C-9'), 13.3 (q, CH_2C-2), 7.8 (q, C-5).

HRMS *m/z* calcd for $C_{13}H_{22}O_4S$ 274.1239, found 274.1240 (EI).



(62a)

(4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-5-methoxymethoxy-4-methylheptan-3-one (62a).[124]

MOM-Cl (0.93 mL, 0.99 g, 12 mmol) was added dropwise over 3 min to a stirred solution of **60ss** (1.0 g, 4.1 mmol) and *i*-Pr_2NEt (2.4 mL, 1.7 g, 13 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C under Ar. The reaction was allowed to warm to ambient temperature with periodic monitoring by TLC (40% ethyl acetate in hexanes). After 3 days (reaction complete by TLC), the mixture was diluted with CH_2Cl_2 (100 mL) and washed sequentially with saturated aq NH_4Cl (×2) and H_2O, dried over Na_2SO_4, concentrated, and fractionated by FCC (15% ethyl acetate in hexanes) to afford **62a** (1.16 g, 98%).

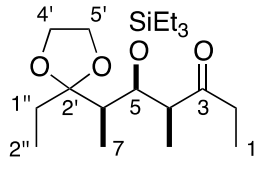
colorless oil, TLC R_f = 0.4 (40% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (1H, d, *J* = 6.5 Hz, HCO_2), 4.54 (1H, d, *J* = 6.5 Hz, HCO_2), 3.97 (1H, dd, *J* = 3, 5 Hz, HC-5), 3.95-3.90 (4H, m, H_2C-4′, H_2C-5′), 3.32 (3H, s, H_3CO), 2.81 (1H, dq, *J* = 5, 7 Hz, HC-4), 2.65 (1H, dq, *J* = 18, 7 Hz, H_2C-2), 2.44 (1H, dq, *J* = 18, 7 Hz, H_2C-2), 1.91 (1H, dq, *J* = 3, 7 Hz, HC-6), 1.69-1.57 (2H, m, H_2C-1″), 1.06 (3H, d, *J* = 7 Hz, H_3CC-4), 1.01 (3H, t, *J* = 7 Hz, H_3C-1), 0.87 (3H, d, *J* = 7 Hz, H_3C-7), 0.83 (3H, t, *J* = 7.5 Hz, H_3C-2″).

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7 (s, C-3), 113.5 (s, C-2′), 97.4 (t, OCH_2O), 77.7 (d, C-5), 65.2 (t ┤ 2, C-4′, C-5′), 56.4 (t, CH_3O), 51.2 (d, C-4), 41.5 (d, C-6), 35.6 (t, C-2), 26.8 (t, C-1″), 12.0 (q, CH_3C-4), 10.5 (q, C-7), 7.9 (q, C-1), 7.6 (q, C-2″).

HRMS *m/z* calcd. for $C_{15}H_{28}O_5$+Na^+ 311.1828, found 311.1827 (ESI).



(62b)

(4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-4-methyl-5-((triethylsilyl)oxy)heptan-3-one (62b).[124]

Imidazole (418 mg, 6.14 mmol) and Et_3SiCl (0.89 mL, 0.80 g, 5.3 mmol) were sequentially added to a stirred solution of **60ss** (1.0 g, 4.1 mmol) in DMF (6.0 mL) at room temperature under argon. After 16 h, the mixture was diluted with ethyl acetate, washed sequentially with saturated aq NH_4Cl and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (5% ethyl acetate in hexanes) to afford the title compound (1.43 g, 97%). Spectroscopic data were consistent with those previously reported for (–)-**62b**.[109]

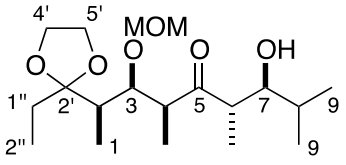
colorless viscous oil, TLC R_f = 0.3 (10% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (1H, br dd, *J* = 3, 4 Hz, HC-5), 3.95-3.87 (4H, m, H_2C-4′, H_2C-5′), 2.75 (1H, dq, *J* = 4, 6.5 Hz, HC-4), 2.64 (1H, dq, *J* = 18, 7 Hz, HC-2), 2.41 (1H, dq, *J* = 18, 7 Hz, HC-2), 1.85 (1H, dq, *J* = 3, 7 Hz, HC-6), 1.68 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1″), 1.59 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1″), 1.03 (3H, d, *J* = 6.5 Hz, H_3CC-4), 1.02 (3H, t, *J* = 7.5 Hz, H_3C-1), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.84 (3H, t, *J* = 7 Hz, H_3C-2″), 0.83 (3H, d, *J* = 7 Hz, H_3CC-6), 0.62 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1 (s, C-3), 113.8 (s, C-2′), 72.9 (d, C-5), 65.2 (t, C-4′), 65.1 (t, C-5′), 52.7 (d, C-4), 41.9 (d, C-6), 36.4 (t, C-2), 26.9 (t, C-1″), 12.5 (q, CH_3C-4), 10.6 (q, CH_3C-6), 7.8 (q, C-2″), 7.4 (q, C-1), 7.3 (q ×3, CH_3CSi), 5.6 (t ×3, CH_2Si).

HRMS *m/z* calcd. for $C_{19}H_{38}O_4Si+Na^+$ 381.2431, found 381.2444 (ESI).



(71aa; Pg = MOM)

(2*R*,3*S*,4*S*,6*S*,7*S*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(methoxymethoxy)-4,6,8-trimethylnonan-5-one (71aa, Pg = MOM).[124]

n-Butyllithium (2.5 M in hexanes; 0.048 mL, 0.12 mmol) was added dropwise to a stirred solution of *t*-butyl(trimethylsilyl)amine (0.026 mL, 20 mg, 0.14 mmol) in THF (0.4 mL) at 0 °C. The ice bath was removed and, after 15 min, a solution of **62a** (Pg = MOM) (30 mg, 0.10 mmol) in THF (0.6 mL) was added dropwise via syringe. After 5 min, the mixture was cooled to –78 °C (note: quenching the reaction with TMSCl at this point gave a 3.4:1 mixture of (*E*)- and (*Z*)-enol silanes, respectively) and *i*-PrCHO (0.052 mL, 41 mg, 0.57 mmol) was added. After 10 min, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR indicated the presence of a 12:5:3:2 mixture of **71aa** (Pg = MOM), **71sa** (Pg = MOM), **71as** (Pg = MOM), and **71ss** (Pg = MOM), respectively. Fractionation of the crude by FCC (20-40% ethyl acetate in hexanes) gave **71sa** (Pg = MOM) (9 mg, 24%), **71as** (Pg = MOM) (3 mg, 8%), and 5:1 mixture of **71aa** (Pg = MOM) and **71ss** (Pg = MOM), respectively (16 mg, 43%) that was further fractionated by PTLC (10% acetone in hexanes) to afford a 1.2:1 mixture of **71aa** (Pg = MOM) and **71ss** (Pg = MOM), respectively (7 mg, 19%) and the title compound **71aa** (Pg = MOM) (8 mg, 21%).

colorless oil, TLC R_f = 0.34 (20% acetone in hexanes).

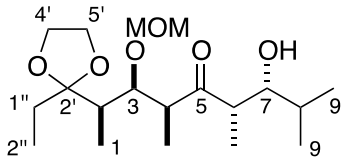
IR (DRIFT) ν_{max} 3502, 1705 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (1H, d, *J* = 6.5 Hz, HCO_2), 4.58 (1H, d, *J* = 6.5 Hz, HCO_2), 4.05 (1H, dd, *J* = 3, 5.5 Hz, HC-3), 3.97-3.94 (4H, m, H_2C-4′, H_2C-5′), 3.43 (1H, ddd, *J* = 4.5, 6.5, 7 Hz, HC-7), 3.36 (3H, s, H_3CO), 3.01 (1H, dq, *J* = 5.5, 7 Hz, HC-4), 2.96 (1H, dq, *J* = 7, 7 Hz, HC-6), 2.40 (1H, d, *J* = 6.5 Hz, HO), 1.94 (1H, dq, *J* = 3, 7 Hz, HC-2), 1.76-1.63 (3H, m, HC-8, H_2C-1″), 1.13 (3H, d, *J* = 7 Hz, H_3CC-4), 1.09 (3H, d, *J* = 7 Hz, H_3CC-6), 0.96 (3H, d, *J* = 6.5 Hz,

H_3C-9), 0.94 (3H, d, *J* = 7 Hz, H_3C-1), 0.90 (3H, d, *J* = 6.5 Hz, H_3C-9′), 0.86 (3H, t, *J* = 7.5 Hz, H_3C-2″).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.6 (s, C-5), 113.6 (s, C-2′), 97.5 (t, OCH_2O), 78.9 (d, C-7), 76.5 (d, C-3), 65.3 (t, C-4′), 65.2 (t, C-5′), 56.5 (q, CH_3O), 52.0 (d, C-4), 48.1 (d, C-6), 42.3 (d, C-2), 30.4 (d, C-8), 27.0 (t, C-1″), 20.3 (q, C-9), 15.8 (q, C-9′), 14.2 (q, CH_3C-6), 12.4 (q, CH_3C-4), 10.4 (q, C-1), 7.7 (q, C-2″).

HRMS *m/z* calcd. for $C_{19}H_{36}O_6$+Na^+ 383.2404, found 383.2396 (ESI).



(71as; Pg = MOM)

(2*R*,3*S*,4*S*,6*S*,7*R*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(methoxymethoxy)-4,6,8-trimethylnonan-5-one (71as, Pg = MOM).[124]

A solution of **62a** (33 mg, 0.11 mmol) in THF (0.6 mL) was added dropwise via syringe to a stirred solution of freshly prepared LiHMDS (0.34 M in THF, 0.5 mL, 0.17 mmol) at –42 °C under Ar. After 1.5 h, the mixture was cooled to –78 °C (note: quenching the reaction with TMSCl at this point gave a 10:1 mixture of (*Z*)- and (*E*)-enol silanes, respectively) and *i*-PrCHO (52 µL, 41 mg, 0.57 mmol) was added via syringe. After 2 min, the reaction was quenched by addition of saturated aq NH_4Cl and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of 20:14:2.5:1:2 mixture of **71as** (Pg = MOM), **71ss** (Pg = MOM), **71aa** (Pg = MOM), **71sa** (Pg = MOM), and **62a**, respectively. Fractionation of the crude by FCC (20-30% ethyl acetate in hexanes) gave a 2.2:1 mixture of **62a** and **71sa** (Pg = MOM), respectively (4 mg), a 1.2:1 mixture of **71ss** (Pg = MOM) and **71aa** (Pg = MOM), respectively (6 mg, 15%), **71ss** (Pg = MOM) (10 mg, 24%), and the titled compound **71as** (Pg = MOM) (18 mg, 44%).

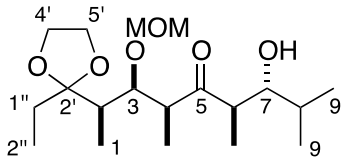
colorless liquid, TLC R_f = 0.4 (35% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3511, 1703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (1H, d, *J* = 6.5 Hz, HCO_2), 4.58 (1H, d, *J* = 6.5 Hz, HCO_2), 4.04 (1H, dd, *J* = 3, 5 Hz, HC-3), 3.95 (4H, br s, H_2C-4′, H_2C-5′), 3.45 (1H, ddd, *J* = 2.5, 3, 8.5 Hz, HC-7), 3.35 (3H, s, H_3CO), 3.02-3.07 (2H, m, HC-4, HC-6), 2.57 (1H, d, *J* = 3 Hz, HO), 1.92 (1H, dq, *J* = 3, 7 Hz, HC-2), 1.73-1.62 (3H, m, H_2C-1″, HC-8), 1.13 (3H, d, *J* = 7 Hz, H_3CC-4), 1.07 (3H, d, *J* = 7 Hz, H_3CC-6), 1.03 (3H, d, *J* = 6.5 Hz, H_3C-9), 0.94 (3H, d, *J* = 7 Hz, H_3C-1), 0.88 (3H, d, *J* = 6.5 Hz, H_3C-9′), 0.86 (3H, t, *J* = 7.5 Hz, H_3C-2″).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.0 (s, C-5), 113.5 (s, C-2′), 97.6 (t, OCH_2O), 77.0 (d, C-3), 76.8 (d, C-7), 65.25 (t, C-4′), 65.23 (t, C-5′), 56.5 (q, CH_3O), 50.4 (d, C-4), 46.9 (d, C-6), 42.2 (d, C-2), 31.1 (d, C-8), 26.9 (t, C-1″), 19.6 (q, C-9), 19.2 (q, C-9′), 12.5 (q, CH_3C-4), 10.6 (q, C-1), 8.7 (q, CH_3C-6), 7.7 (q, C-2″).

HRMS *m/z* calcd. for $C_{19}H_{36}O_6$+Na^+ 383.2404, found 383.2410 (ESI).



(71sa; Pg = MOM)

(2*R*,3*S*,4*S*,6*R*,7*R*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(methoxymethoxy)-4,6,8-trimethylnonan-5-one (71sa; Pg = MOM).[124]

Et_3N (0.064 mL, 46 mg, 0.46 mmol) and (*c*-Hex)$_2$BCl (1.1 M in hexanes; 0.36 mL, 0.40 mmol) were sequentially added via syringe to a stirred solution of **62a** (55mg, 0.19 mmol) in ether (0.5 mL) at 0 °C under argon. After 2 h, the mixture was cooled to –78 °C and *i*-PrCHO (0.088 mL, 70 mg, 0.97 mmol) was added via syringe. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL) with vigorous stirring. The reaction vessel was transferred to an ice bath and after vigorous stirring for 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR indicated the presence of 14:1 mixture of a single aldol adduct (>20:1 dr) and **62a**, respectively. The above mixture (inseparable by chromatography on SiO_2) was taken up in DMF (0.5 mL) and TES-Cl (0.044 mL, 40 mg, 0.26 mmol) and imidazole (22 mg, 0.32 mmol) were added. After 12 h, the

reaction mixture was diluted with ethyl acetate and sequentially washed with saturated aq NH_4Cl and brine. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by FCC (10-20% ethyl acetate in hexanes) to give **62a** (5 mg, 9%) and TES-protected **71sa** (Pg = MOM) (60 mg, 66% from **62a**). The latter was taken up in CH_3CN (4.0 mL) and pyridine (0.41 mL), H_2O (0.018 mL), and HF·pyridine (0.28 mL) were added with stirring. After 4h, the reaction mixture was diluted with ethyl acetate, and sequentially washed with saturated aq $NaHCO_3$, saturated aq $CuSO_4$, and brine. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethyl acetate in hexanes) to afford **71sa** (Pg = MOM) (44 mg, 97%; 64% from **62a**).

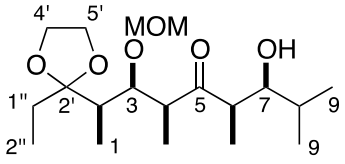
colorless oil, TLC R_f = 0.38 (30% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3474, 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (1H, d, *J* = 7 Hz, HCO_2), 4.51 (1H, d, *J* = 7 Hz, HCO_2), 4.07 (1H, dd, *J* = 3.5, 4.5 Hz, HC-3), 4.04-3.93 (4H, m, H_2C-4′ , H_2C-5′), 3.69 (1H, ddd, *J* = 3, 4.5, 8.5 Hz, HC-7), 3.33 (3H, s, H_3CO), 3.28 (1H, d, *J* = 4.5 Hz, HO), 2.97 (1H, dq, *J* = 3.5, 7 Hz, HC-4), 2.90 (1H, dq, *J* = 8.5, 7 Hz, HC-6), 2.06 (1H, dq, *J* = 4.5, 7.5 Hz, HC-2), 1.77 (1H, dqq, *J* = 3, 7, 7 Hz, HC-8), 1.72-1.61 (2H, m, H_2C-1″), 1.10 (3H, d, *J* = 7 Hz, H_3CC-4), 1.01 (3H, d, *J* = 7 Hz, H_3C-9), 0.98 (3H, d, *J* = 7 Hz, H_3CC-6), 0.96 (3H, d, *J* = 7.5 Hz, H_3C-1), 0.88 (3H, t, *J* = 7.5 Hz, H_3C-2″), 0.87 (3H, d, *J* = 7 Hz, H_3C-9′).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.6 (s, C-5), 113.8 (s, C-2′), 97.6 (t, OCH_2O), 76.4 (d, C-3), 76.2 (d, C-7), 65.3 (t, C-4′), 65.0 (t, C-5′), 56.3 (q, CH_3O), 51.8 (d, C-4), 50.1 (d, C-6), 42.9 (d, C-2), 29.3 (d, C-8), 27.0 (t, C-1″), 20.5 (q, C-9), 14.65 (q, CH_3C-6 or C-9′), 14.63 (q, CH_3C-6 or C-9′), 11.6 (q, C-1), 10.5 (q, CH_3C-4), 8.0 (q, C-2″).

HRMS *m/z* calcd. for $C_{19}H_{36}O_6$+Na^+ 383.2404, found 383.2426 (ESI).



(71ss; Pg = MOM)

(2*R*,3*S*,4*S*,6*R*,7*S*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(methoxymethoxy)-4,6,8-trimethylnonan-5-one (71ss; Pg = MOM).[124]

From the Ti(IV) (*Z*)-enolate of **62a**. Freshly prepared LiHMDS (1.0 M in THF, 0.17 mL, 0.17 mmol) was added dropwise via syringe to a stirred solution of **62a** (44 mg, 0.15 mmol) in THF (0.17 mL) at –42 °C under Ar. After 1.5 h, the mixture was cooled to –78 °C and freshly prepared Ti(O*i*-Pr)$_3$Cl (0.55 M in THF; 0.60 mL, 0.33 mmol) was added. After 15 min, the reaction vessel was transferred to a –42 °C bath and stirring continued for 1 h. The mixture was cooled to –78 °C and *i*-PrCHO (0.068 mL, 54 mg, 0.75 mmol) was added. After 2 h, the reaction was quenched by addition of saturated aq NH_4Cl. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 12:1 mixture of **71ss** (Pg = MOM) and **71as** (Pg = MOM), respectively. Fractionation of the crude by FCC (70% ether in hexanes) gave **71as** (Pg = MOM) (3 mg, 5%) and the title compound (42 mg, 76%). From the (*Z*)-enol borinate of **62a**. Et_3N (0.026 mL, 19 mg, 0.19 mmol) and 9-BBN-OTf (0.5 M in hexanes; 32 mL, 0.16 mmol) were sequentially added via syringe to a stirred solution of **62a** (30 mg, 0.10 mmol) in ether (0.5 mL) at –78 °C under argon. After 2 h, *i*-PrCHO (0.048 mL, 38 mg, 0.52 mmol) was added via syringe. After 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aq H_2O_2 (1 mL) with vigorous stirring. The reaction vessel was transferred to an ice bath and after vigorous stirring for 10 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR indicated the presence of a 14:1 mixture of a single aldol adduct and **62a**, respectively. Fractionation of the crude by FCC (50% ether in hexanes) gave **62a** (2 mg, 7%) and the title compound (29 mg, 77%).

colorless viscous oil, TLC R_f = 0.36 (60% ethyl acetate in hexanes).

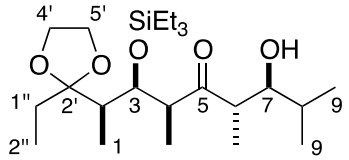
IR (DRIFT) ν_{max} 3500, 1697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (1H, d, *J* = 6.5 Hz, HCO_2), 4.56 (1H, d, *J* = 6.5 Hz, HCO_2), 3.90-3.99 (5H, m, HC-3, H_2C-4′, H_2C-5′), 3.55 (1H, ddd, *J* = 1.5, 2, 9.5 Hz, HC-7), 3.39 (1H, d, *J* = 2 Hz, HO), 3.34 (3H, s, H_3CO), 3.07 (1H, dq, *J* = 4.5, 7 Hz, HC-4), 3.02 (1H, dq, *J* = 1.5, 7.5 Hz, HC-6), 2.03 (1H, dq, *J* = 3, 7 Hz, HC-2), 1.59-1.71 (3H, m, H_2C-1″, HC-8), 1.11 (3H, d, *J* =

7.5 Hz, H_3CC-6), 1.08 (3H, d, *J* = 7 Hz, H_3CC-4), 1.03 (3H, d, *J* = 6.5 Hz, H_3C-9), 0.90 (3H, d, *J* = 7 Hz, H_3C-1), 0.87 (3H, t, *J* = 7.5 Hz, H_3C-2″), 0.83 (3H, d, *J* = 6.5 Hz, H_3C-9′).

^{13}C NMR (125 MHz, $CDCl_3$) δ 219.7 (s, C-5), 113.6 (s, C-2′), 97.4 (t, OCH_2O), 77.4 (d, C-3), 76.1 (d, C-7), 65.2 (d, C-4′), 65.1 (d, C-5′), 56.5 (q, CH_3O), 49.8 (d, C-4), 46.5 (d, C-6), 41.3 (d, C-2), 30.5 (d, C-8), 26.8 (t, C-1″), 19.9 (q, C-9), 18.9 (q, C-9′), 12.0 (q, CH_3C-4), 10.8 (q, C-1), 9.3 (q, CH_3C-6), 7.8 (q, C-2″).

HRMS *m/z* calcd. for $C_{19}H_{36}O_6$+Na^+ 383.2404, found 383.2395 (ESI).



(71aa; Pg = TES)

(2*R*,3*S*,4*S*,6*S*,7*S*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(triethylsilyloxy)-4,6,8-trimethylnonan-5-one (71aa; Pg = TES).[124]

n-Butyllithium (2.5 M in hexanes; 0.040 mL, 0.10 mmol) was added dropwise to a stirred solution of *t*-butyl(trimethylsilyl)amine (0.021 mL, 16 mg, 0.11 mmol) in THF (0.41 mL) at 0 °C. The ice bath was removed and, after 15 min, a solution of **62b** (30 mg, 0.084 mmol) in THF (0.6 mL) was added dropwise via syringe. After 5 min, the mixture was cooled to –78 °C (note: quenching the reaction with TMSCl at this point gave a 2.8:1 mixture of (*E*)- and (*Z*)-enol silanes, respectively) and *i*-PrCHO (0.042 mL, 33 mg, 0.46 mmol) was added. After 10 min, the reaction was quenched by addition of saturated aq NH_4Cl and the mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR indicated the presence of a 5:4:2:1 mixture of **71aa** (Pg = TES), **71sa** (Pg = TES), **71as** (Pg = TES), and **71ss** (Pg = TES), respectively. Fractionation of the crude by FCC (20-40% ether in hexanes) gave **71as** (Pg = TES) (7 mg, 19%), **71sa** (Pg = TES) (6 mg, 17%), a 3:2:1 mixture of **71sa** (Pg = TES), **71aa** (Pg = TES), and **71ss** (Pg = TES), respectively (7 mg, 19%), and a 10:1:0.3 mixture of **71aa** (Pg = TES), **71ss** (Pg = TES), and **71sa** (Pg = TES), respectively (8 mg, 22%). The latter fraction was subjected to PTLC (30% ether in hexanes) to obtain the title compound (5 mg, 14%; dr >15).

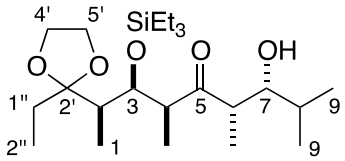
colorless liquid, TLC R_f = 0.45 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3518, 1704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 (1H, dd, *J* = 3, 5.5 Hz, HC-3), 3.97-3.86 (4H, m, H_2C-4′, H_2C-5′), 3.41 (1H, ddd, *J* = 5, 6.5, 7 Hz, HC-7), 2.98 (1H, dq, *J* = 5.5, 7 Hz, HC-4), 2.91 (1H, dq, *J* = 7, 7 Hz, HC-6), 2.45 (1H, d, *J* = 6.5 Hz, HO), 1.87 (1H, dq, *J* = 3, 7 Hz, HC-2), 1.72 (1H, dqq, *J* = 5, 6.5, 6.5 Hz, HC-8), 1.72-1.56 (2H, m, H_2C-1″), 1.09 (3H, d, *J* = 7 Hz, H_3CC-6), 1.08 (3H, d, *J* = 7 Hz, H_3CC-4), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.96 (3H, d, *J* = 6.5 Hz, H_3C-9), 0.91 (3H, d, *J* = 6.5 Hz, H_3C-9′), 0.88 (3H, d, *J* = 7 Hz, H_3C-1), 0.85 (3H, t, *J* = 7.5 Hz, H_3C-2″), 0.65 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 219.7 (s, C-5), 113.8 (s, C-2′), 78.9 (d, C-7), 71.9 (d, C-3), 65.2 (t, C-4′), 65.0 (t, C-5′), 52.9 (d, C-4), 48.4 (d, C-6), 42.4 (d, C-2), 30.6 (d, C-8), 27.3 (t, C-1″), 20.3 (q, C-9), 16.1 (q, C-9′), 14.3 (q, CH_3C-6), 13.3 (q, CH_3C-4), 10.3 (q, C-1), 7.6 (q, C-2″), 7.3 (q ×3, CH_3CSi), 5.6 (t ×3, CH_2Si).

HRMS *m/z* calcd. for $C_{23}H_{46}O_5Si+Na^+$ 453.3006, found 453.2986 (ESI).



(71as; Pg = TES)

(2*R*,3*S*,4*S*,6*S*,7*R*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(triethylsilyloxy)-4,6,8-trimethylnonan-5-one (71as; Pg = TES).[124]

A solution of **62b** (32 mg, 0.089 mmol) in THF (0.6 mL) was added dropwise via syringe to a stirred solution of freshly prepared LiHMDS (0.27 M in THF, 0.49 mL, 0.13 mmol) at –42 °C under Ar. After 1.5 h (note: quenching the reaction with TMSCl at this point gave a 10:1 mixture of (*Z*)- and (*E*)-enol silanes, respectively), the mixture was cooled to –78 °C and *i*-PrCHO (42 µL, 33 mg, 0.46 mmol) was added via syringe. After 2 min, the reaction was quenched by addition of saturated aq NH_4Cl and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence

of a 14:7:1.5:0.5:1 mixture of **71as** (Pg = TES), **71ss** (Pg = TES), **71aa** (Pg = TES), **71sa** (Pg = TES), and **62b**, respectively. Fractionation of the crude by FCC (10-20% ethyl acetate in hexanes) gave **62b** (2 mg, 7%), a 15:5:1 mixture of **71ss** (Pg = TES), **71aa** (Pg = TES), and **71sa** (Pg = TES), respectively (13 mg, 34%), a 3:1:1 mixture of **71as** (Pg = TES), **71sa** (Pg = TES), and **71aa** (Pg = TES), respectively (3 mg, 8%), and the title compound (16 mg, 42%).

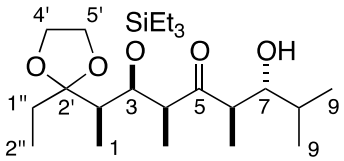
colorless viscous oil, TLC R_f = 0.3 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3514, 1700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (1H, dd, *J* = 3.5, 5 Hz, HC-3), 3.86-3.95 (4H, m, H_2C-4′, H_2C-5′), 3.43 (1H, br d, *J* = 9 Hz, HC-7), 3.00 (1H, dq, *J* = 5, 7 Hz, HC-4), 2.96 (1H, dq, *J* = 2, 7 Hz, HC-6), 2.74 (1H, br s, HO), 1.85 (1H, dq, *J* = 3.5, 7 Hz, HC-2), 1.73-1.58 (3H, m, H_2C-1″, HC-8), 1.09 (3H, d, *J* = 7 Hz, H_3CC-4), 1.06 (3H, d, *J* = 7 Hz, H_3CC-6), 1.03 (3H, d, *J* = 6.5 Hz, H_3C-9), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.88 (3H, d, *J* = 7 Hz, H_3C-1), 0.87 (3H, d, *J* = 6.5 Hz, H_3C-9′), 0.84 (3H, t, *J* = 7.5 Hz, H_3C-2″), 0.63 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 219.2 (s, C-5), 113.7 (s, C-2′), 76.5 (d, C-7), 71.9 (d, C-3), 65.2 (t, C-4′), 65.1 (t, C-5′), 51.6 (d, C-4), 46.8 (d, C-6), 42.6 (d, C-2), 31.0 (d, C-8), 27.2 (t, C-1″), 19.7 (q, C-9), 19.1 (q, C-9′), 13.2 (q, CH_3C-4), 10.7 (q, C-1), 8.8 (q, CH_3C-6), 7.6 (q, C-2″), 7.3 (q ×3, CH_3CSi), 5.6 (t ×3, CH_2Si).

HRMS *m/z* calcd. for $C_{23}H_{46}O_5Si+Na^+$ 453.3006, found 453.3000 (ESI).



(71sa; Pg = TES)

(2*R*,3*S*,4*S*,6*R*,7*R*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(triethylsilyloxy)-4,6,8-trimethylnonan-5-one (71sa; Pg = TES).[124]

Freshly prepared LiHMDS (0.91 M in THF; 0.11 mL, 0.10 mmol) was added dropwise via syringe to a stirred solution of **62b** (32 mg, 0.089 mmol) in THF (0.4 mL) at −50 °C, under Ar.

After 1.5 h, the reaction mixture was cooled to −78 °C and (*c*-Hex)$_2$BCl (1.1 M in hexanes; 0.13 mL, 0.14 mmol) was added. After 15 min, the reaction vessel was transferred to a −50 °C bath and stirring continued for 2 h. The mixture was cooled to −78 °C and a solution of *i*-PrCHO (0.041 mL, 32 mg, 0.45 mmol in THF (0.30 mL) was added. After 5 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 1 mL), MeOH (0.25 mL), and 30% aqueous H_2O_2 (0.40 mL). The reaction vessel was transferred to an ice bath and after vigorous stirring for 30 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 9:1 mixture of a single aldol adduct and **62b**, respectively. Fractionation of the crude product PTLC (50% Et_2O in hexanes) afforded recovered **62b** (2 mg, 6%) and the titled compound (32 mg, 83%).

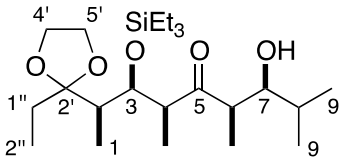
colorless oil, TLC R_f = 0.42 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3508, 1706 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (1H, dd, *J* = 5, 5.5 Hz, HC-3), 3.95 - 3.88 (4H, m, H_2C-4′, H_2C-5′), 3.46 (1H, ddd, *J* = 4.5, 6.5, 7 Hz, HC-7), 2.99 (1H, dq, *J* = 5, 7 Hz, HC-4), 2.90 (1H, dq, *J* = 7, 7 Hz, HC-6), 2.61 (1H, d, *J* = 6.5 Hz, HO), 1.94 (1H, dq, *J* = 5.5, 7 Hz, HC-2), 1.73 (1H, dqq, *J* = 4.5, 6.5 Hz, HC-8), 1.68 (1H, dq, *J* = 14, 7.5 Hz, HC-1″), 1.58 (1H, dq, *J* = 14, 7.5 Hz, HC-1″), 1.10 (3H, d, *J* = 7 Hz, H_3CC-6), 1.09 (3H, d, *J* = 7 Hz, H_3CC-4), 0.97 (3H, d, *J* = 6.5 Hz, H_3C-9), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.91 (3H, d, *J* = 6.5 Hz, H_3C-9′), 0.90 (3H, d, *J* = 7 Hz, H_3C-1), 0.85 (3H, t, *J* = 7,5 Hz, H_3C-2″), 0.64 (6H, ap q, *J* = 8 Hz, CH_2Si ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 219.3 (s, C-5), 113.8 (s, C-2′), 78.4 (d, C-7), 72.0 (d, C-3), 65.14 (t, C-4′), 65.11 (t, C-5′), 52.5 (d, C-4), 48.9 (d, C-6), 42.2 (d, C-2), 30.3 (d, C-8), 27.2 (t, C-1″), 20.3 (q, C-9), 16.0 (q, C-9′), 14.6 (q, CH_3C-6), 13.0 (q, CH_3C-4), 10.9 (q, C-1), 7.6 (q, C-2″), 7.3 (q ×3, CH_3CSi), 5.6 (t ×3, CH_2Si).

HRMS *m/z* calcd. for $C_{23}H_{46}O_5Si+Na^+$ 453.3006, found 453.2998 (ESI).



(71ss; Pg = TES)

(2*R*,3*S*,4*S*,6*R*,7*S*)-*rel*-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(triethylsilyloxy)-4,6,8-trimethylnonan-5-one (71ss; Pg = TES).[124]

From the (*Z*)-enol borinate of **62b**. A solution of **62b** (33 mg, 0.092 mmol) in Et_2O (0.6 mL) was added dropwise via syringe to a stirred solution of Et_3N (0.024 mL, 17 mg, 0.17 mmol) and 9-BBN-OTf (0.5 M in hexanes; 0.28 mL, 0.14 mmol) in Et_2O (0.6 mL) at –78 °C under argon. After 6 h, *i*-PrCHO (0.042 mL, 33 mg, 0.46 mmol) was added and, after 2 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aqueous H_2O_2 (1 mL). The reaction vessel was transferred to an ice bath and after vigorous stirring for 20 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of 4:1 mixture of a single aldol adduct (dr >20:1) and **62b**, respectively. Fractionation of the crude by FCC (15% ethyl acetate in hexanes) gave recovered **62b** (6 mg, 18%) and the title compound (26 mg, 67%). From the Ti(IV) (*Z*)-enolate of **62b**. Freshly prepared LiHMDS (1.0 M in THF, 0.12 mL, 0.12 mmol) was added dropwise via syringe to a stirred solution of **62b** (41 mg, 0.11 mmol) in THF (0.11 mL) at –42 °C under Ar. After 75 min, the mixture was cooled to –78 °C and freshly prepared $TiCl(O\textit{i}\text{-}Pr)_3$ (0.55 M in THF; 0.44 mL 0.24 mmol) was added. After 15 min, the reaction vessel was transferred to a –42 °C bath and stirring continued for 90 min. The mixture was cooled to –78 °C and *i*-PrCHO (0.050 mL, 39 mg, 0.54 mmol) was added. After 3 h, the reaction was quenched by addition of saturated aq NH_4Cl. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 15:1 mixture of **71ss** (Pg = TES) and **71as** (Pg = TES), respectively. Fractionation of the crude by PTLC (80% ether in hexanes) gave **71as** (Pg = TES) (2 mg, 4%) and the title compound (35 mg, 71%).

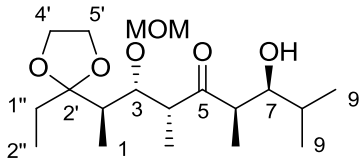
colorless oil, TLC R_f = 0.41 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3522, 1691 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (1H, dd, *J* = 3, 4 Hz, HC-3), 3.95-3.88 (4H, m, H_2C-4′, H_2C-5′), 3.51 (1H, ddd, *J* = 1.5, 2, 9.5 Hz, HC-7), 3.43 (1H, d, *J* = 2 Hz, HO), 3.00 (1H, dq, *J* = 4, 7 Hz, HC-4), 2.99 (1H, dq, *J* = 1.5, 7.5 Hz, HC-6), 1.91 (1H, dq, *J* = 3, 7 Hz, HC-2), 1.70-1.53 (3H, m, HC-8, H_2C-1″), 1.10 (3H, d, *J* = 7.5 Hz, H_3CC-6), 1.03 (3H, d, *J* = 6.5 Hz, H_3C-9), 1.01 (3H, d, *J* = 7 Hz, H_3CC-4), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.85 (3H, t, *J* = 7.5 Hz, H_3C-2″), 0.820 (3H, d, *J* = 6.5 Hz, H_3C-9′), 0.815 (3H, d, *J* = 7 Hz, H_3C-1), 0.63 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 220.4 (s, C-5), 113.7 (s, C-2′), 76.3 (d, C-7), 73.0 (d, C-3), 65.1 (t, C-4′), 65.0 (t, C-5′), 51.3 (d, C-4), 47.3 (d, C-6), 41.0 (d, C-2), 30.4 (d, C-8), 26.8 (t, C-1″), 19.9 (q, C-9), 18.9 (q, C-9′), 13.1 (q, CH_3C-4), 10.5 (q, C-1), 9.3 (q, CH_3C-6), 7.5 (q, C-2″), 7.3 (q ×3, CH_3CSi), 5.5 (t ×3, CH_2Si).

HRMS *m/z* calcd. for $C_{23}H_{46}O_5Si+Na^+$ 453.3006, found 453.3013 (ESI).

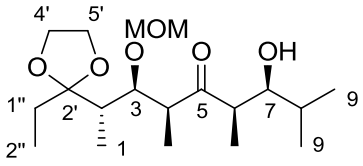


(73as; Pg = MOM)

(2*R*,3*R*,4*R*,6*R*,7*S*)-*rel*-2-(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(methoxymethoxy)-4,6,8-trimethylnonan-5-one (73as; Pg = MOM).

i-Pr_2EtN (0.25 mL, 185 mg, 1.43 mmol) and MOM-Cl (0.10 mL, 106 mg, 1.32 mmol) were added to a stirred solution of a 3:1 mixture of 1:3 mixture of **117ssa** and **117asa** (5 mg, 0.017 mmol) in CH_2Cl_2 (50 μL) at 0 °C. The mixture was allowed to warm to ambient temperature, and reaction progress was monitored by TLC. After 12 h, the reaction mixture was diluted with satd. aq. NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. The crude product that was fractionated by PTLC (60% Et_2O in hexanes) to afford a 1:3 mixture of **148ssa** and **148asa** (5 mg, 91%), respectively. 70% HF·Py (0.1 mL) was added to a stirred solution of 1:3 mixture of **148ssa** and **148asa** (5 mg 0.01 mmol) in acetonitrile (0.5 mL) at room temperature and reaction progress was monitored by TLC. After 1 h, the reaction was quenched with satd. aq. $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4

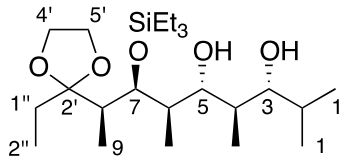
and concentrated to afford the crude product (3 mg). The ^{1}H NMR of the crude product showed presence of a 1:3 mixture of **149ssa** and **149asa**, respectively. A suspension of Raney nickel (W2; 0.2 mL settled volume) in EtOH (1.0 mL) was added to a 1:3 mixture of **149ssa** and **149asa** (3 mg) and the mixture was heated under reflux with vigorous stirring. After 4 h (reaction was complete by TLC analysis), the mixture was decanted and the solid was suspended in EtOH (3 mL) and heated under reflux with vigorous stirring for several 15 min. This washing procedure was repeated with ethyl acetate (×1), and acetone (×2). The combined organic layers were filtered through Celite®, concentrated, and fractionated by FCC (40% ethyl acetate in hexanes) to give 1:3 mixture of **73ss** (Pg = MOM) and **73as** (Pg = MOM) (2 mg, 47% over 2 steps), respectively. The ^{1}H and ^{13}C NMR data of the major product (i.e., **73as** (Pg = MOM)) in the 1:3 mixture closlely matched with those previously reported.[124]



(73ss; Pg = MOM)

(2*S*,3*S*,4*S*,6*R*,7*S*)-*rel*-2-(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(methoxymethoxy)-4,6,8-trimethylnonan-5-one (73as; Pg = MOM).

The minor product in the 1:3 mixture of **73ss** and **73as** (see the preparation of **73ss** (Pg = MOM)). The ^{1}H and ^{13}C NMR data of the minor product (i.e., **73ss** (Pg = MOM)) in the 1:3 mixture closlely matched with those previously reported.[124]



(77)

(3*R*,4*R*,5*R*,6*R*,7*S*,8*R*)-*rel*-8-(2-Ethyl-1,3-dioxolan-2-yl)-2,4,6-trimethyl-7-((triethylsilyl)oxy)nonane-3,5-diol (77).[124]

DIBAL-H (1 M in toluene; 0.35 mL, 0.35 mmol) was added dropwise via syringe to a stirring solution of the **71sa** (Pg = TES) (50 mg, 0.12 mmol) in THF (1.6 mL) at –78 °C under Ar.

After 2 h, additional DIBAL-H (1 M in toluene; 0.12 mL, 0.12 mmol) was added. After 1 h, the reaction was quenched by addition of MeOH (0.6 mL) and the mixture was allowed to warm to room temperature over 20 min. Saturated aq Rochelle′s salt (0.98 mL) was added and, after vigorous stirring for 30 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (15% ethyl acetate in hexanes) to give the title compound (32 mg, 63%).

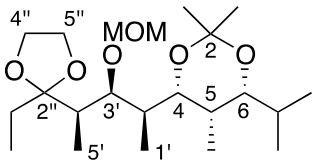
colorless oil, TLC R_f = 0.4 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3434 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (1H, br s, HOC-5), 4.15 (1H, br s, HC-7), 3.90-4.00 (4H, m, H_2C-4′, H_2C-5′), 3.59 (1H, br dd, *J* = 4, 8 Hz, HC-5), 3.55 (1H, br s, HOC-3), 3.49 (1H, br d, *J* = 7.5 Hz, HC-3), 2.12 (1H, br dq, *J* = 8, 7 Hz, HC-6), 1.96 (1H, dq, *J* = 2 Hz, HC-8), 1.69 (1H, dq, *J* = 15, 7.5 Hz, HCC-2′), 1.58 (1H, dq, *J* = 15, 7.5 Hz, HCC-2′), 1.04 (3H, d, *J* = 7 Hz, H_3C-9), 1.00 (3H, d, *J* = 7 Hz, H_3C-1), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.90 (3H, d, *J* = 7 Hz, H_3CC-4), 0.89 (3H, d, *J* = 7 Hz, H_3C-1), 0.88 (3H, d, *J* = 7 Hz, H_3CC-6), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2′), 0.67 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 114.1 (s, C-2′), 80.7 (d, C-5), 79.1 (d, C-3), 74.9 (d, C-7), 65.1 (t, C-4′), 65.0 (t, C-5′), 44.5 (d, C-6), 39.9 (d, C-8), 38.6 (d, C-4), 30.4 (d, C-2), 26.6 (t, CH_2C-2′), 20.7 (q, C-1), 16.6 (q, C-4), 15.0 (q, C-1), 13.4 (q, C-6), 11.5 (q, C-9), 7.6 (q, CH_3CC-2′), 7.2 (q ×3, CH_3CSi), 5.4 (t ×3, CH_2Si).

HRMS *m/z* calcd. for $C_{23}H_{48}O_5Si+Na^+$ 455.3163, found 455.3152 (ESI).



(78)

(4*S*,5*S*,6*R*)-*rel*-4-((2*S*,3*S*,4*R*)-4-(2-Ethyl-1,3-dioxolan-2-yl)-3-(methoxymethoxy)pentan-2-yl)-6-isopropyl-2,2,5-trimethyl-1,3-dioxane (78).[124]

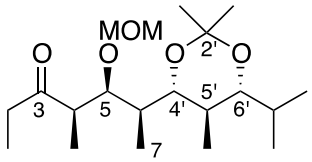
DIBAL-H (1 M in cyclohexane; 0.076 mL, 0.076 mmol) was added dropwise via syringe to a stirred solution of **71as** (Pg = MOM) (11 mg, 0.030 mmol) in dry THF (0.5 mL) at –78 °C. After 1 h, the reaction was quenched by addition of MeOH (1 mL) and the mixture was allowed to warm ambient temperature. Aqueous Rochelle′s salt (1 M) was added and after vigorous stirring for 30 min, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to get the crude diol (dr >10 by ^{1}H NMR). The diol was taken up in acetone (0.7 mL) and 2,2-dimethoxypropane (0.3 mL) and *p*-TsOH·H_2O (2 mg) were added to the stirred solution at 0 °C. The reaction mixture was allowed to warm up to room temperature and after 15 min, saturated aq $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by PTLC (15% ethyl acetate in hexanes) to give the title compound (8 mg, 65%).

colorless viscous oil, TLC R_f = 0.63 (20% ethyl acetate in hexanes).

^{1}H NMR (500 MHz, C_6D_6) δ 4.81 (1H, d, *J* = 6 Hz, HCO_2), 4.68 (1H, d, *J* = 6 Hz, HCO_2), 4.20 (1H, br d, *J* = 6 Hz, HC-3′), 3.86 (1H, dd, *J* = 2, 10 Hz, HC-4), 3.51-3.73 (4H, m, H_2C-4′, H_2C-5′), 3.30 (1H, dd, *J* = 2, 9.5 Hz, HC-6), 3.29 (3H, s, H_3CO), 2.19 (1H, dq, *J* = 6, 7.5 Hz, HC-4′), 2.07 (1H, br dq, *J* = 9, 7 Hz, HC-2′), 1.73-1.81 (3H, m, H_2CC-2″, HCC-6), 1.57 (1H, ddq, *J* = 2, 2, 7 Hz, HC-5), 1.49 (3H, s, H_3CC-2), 1.47 (3H, s, H_3CC-2), 1.23 (3H, d, *J* = 7.5 Hz, H_3C-5′), 1.08 (3H, d, *J* = 6.5 Hz, H_3CCC-6), 0.98 (3H, t, *J* = 7.5 Hz, H_3CCC-2″), 0.966 (3H, d, *J* = 6.5 Hz, H_3CC-5), 0.963 (3H, d, *J* = 7 Hz, H_3C-1′), 0.69 (3H, d, *J* = 7 Hz, H_3CCC-6).

^{13}C NMR (125 MHz, C_6D_6) δ 114.4 (s, C-2″), 99.29 (s, C-2), 99.21 (t, OCH_2O), 80.2 (d, C-6), 77.6 (d, C-3′), 75.0 (d, C-4), 65.9 (t, C-4″), 65.4 (t, C-5″), 56.1 (q, CH_3O), 44.2 (d, C-4′), 41.7 (d, C-2′), 31.3 (d, C-5), 30.8 (q, CH_3C-2), 30.1 (d, CHC-6), 28.4 (t, CH_2C-2″), 20.5 (q, CH_3CC-6), 20.4 (q, CH_3C-2), 17.8 (q, CH_3CC-6), 12.8 (q, C-5′), 8.8 (q, C-1′), 8.4 (q, CH_3CC-2″), 5.2 (q, CH_3C-5).

HRMS *m/z* calcd. for $C_{22}H_{42}O_6$+Na^+ 425.2873, found 425.2887 (ESI).



(79)

(4*R*,5*S*,6*S*)-*rel*-6-((4*S*,5*R*,6*R*)-6-Isopropyl-2,2,5-trimethyl-1,3-dioxan-4-yl)-5-(methoxymethoxy)-4-methylheptan-3-one (79).[124]

DIBAL-H (1 M in cyclohexane; 0.21 mL, 0.21 mmol) was added dropwise via syringe to a stirring solution of **71sa** (Pg = MOM) (30 mg, 0.083 mmol) in dry THF (1.0 mL) at –78 °C. After 30 min, the reaction was quenched by addition of MeOH (1 mL) and the mixture was allowed to warm ambient temperature. Aqueous Rochelle′s salt (1 M) was added and after vigorous stirring for 30 min, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 17:1 mixture of diols. Fractionation of the crude by FCC (50% ethyl acetate in hexanes) provided the syn diol **76** (23 mg, 76%). The above diol **76** (23 mg, 0.06 mmol) was taken up in acetone (1.0 mL) and 2,2-dimethoxypropane (0.1 mL) and *p*-TsOH·H_2O (0.03 M in acetone, 0.03 mL) were added to the stirring solution at room temperature. After 2 h, the reaction was quenched by addition of saturated aq $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated to give a crude mixture of acetonides (ketal and ketone; 24 mg) whose ^{1}H NMR spectrum showed insufficient chemical shift dispersion for NOE studies. The crude acetonide mixture (8.5 mg, 0.02 mmol) was taken up in acetone (2.0 mL) and *p*-TsOH·H_2O (4 mg) was added to the stirred solution at room temperature. After 4 h, the reaction was quenched by addition of saturated aq $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by PTLC (15% ethyl acetate in hexanes) to give the title compound (7 mg, 92%; 70% from **71sa** (Pg = MOM)).

colorless liquid, TLC R_f = 0.46 (15% ethyl acetate in hexanes).

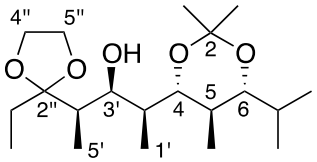
IR (DRIFT) ν_{max} 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (1H, d, *J* = 6.5 Hz, HCO_2), 4.52 (1H, d, *J* = 6.5 Hz, HCO_2), 4.01 (1H, dd, *J* = 2.5, 5.5 Hz, HC-5), 3.35 (3H, s, H_3CO), 3.32 (1H, dd, *J* = 2, 10.5 Hz, HC-4′),

3.27 (1H, dd, J = 2, 10 Hz, HC-6′), 2.81 (1H, dq, J = 5.5, 7 Hz, HC-4), 2.67 (1H, dq, J = 18, 7 Hz, HC-2), 2.49 (1H, dq, J = 18, 7.5 Hz, HC-2), 1.87 (1H, dqq, J = 2, 7, 7 Hz, HCC-6′), 1.81 (1H, ddq, J = 2, 2.5, 7 Hz, HC-6), 1.58 (1H, ddq, J = 10, 10.5, 6.5 Hz, HC-5′), 1.34 (3H, s, H_3CC-2′), 1.33 (3H, s, H_3CC-2′), 1.12 (3H, d, J = 7 Hz, H_3CC-4), 1.04 (3H, t, J = 7 Hz, H_3C-1), 0.94 (3H, d, J = 7 Hz, H_3C-7), 0.93 (3H, d, J = 7 Hz, H_3CC-6′), 0.85 (3H, d, J = 7 Hz, H_3CC-6′), 0.69 (3H, d, J = 6.5 Hz, H_3CC-5′).

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9 (s, C-3), 97.9 (s, C-2′), 97.9 (t, OCH_2O), 78.6 (d, C-4′), 78.0 (d, C-5), 78.0 (d, C-6′), 56.4 (q, CH_3O), 51.3 (d, C-4), 36.9 (d, C-6), 35.8 (t, C-2), 32.9 (d, C-5′), 30.1 (q, CH_3C-2′), 28.4 (d, CHC-6′), 20.4 (q, CH_3CC-6′), 19.3 (q, CH_3C-2′), 14.6 (q, CH_3CC-6′), 14.3 (q, C-7), 12.6 (q, CH_3C-4), 12.2 (q, CH_3C-5′), 7.9 (q, C-1).

HRMS *m/z* calcd. for $C_{20}H_{38}O_5$+Na^+ 381.2617, found 381.2620 (ESI).



(80)

(4*S*,5*R*,6*R*)-*rel*-4-((2*S*,3*S*,4*R*)-4-(2-Ethyl-1,3-dioxolan-2-yl)-3-(methoxymethoxy)pentan-2-yl)-6-isopropyl-2,2,5-trimethyl-1,3-dioxane (80).[124]

2,2-Dimethoxypropane (0.2 mL, excess) and *p*-TsOH·H_2O (2 mg, 0.01 mmol) were added to a solution of **77** (25 mg, 0.058 mmol) in CH_2Cl_2 (0.85 mL) at –42 °C under Ar. After 1 h, the mixture was diluted with CH_2Cl_2, washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (10% ethyl acetate in hexanes) to give the title compound (11 mg, 53%; 33% from **71sa** (Pg = TES)).

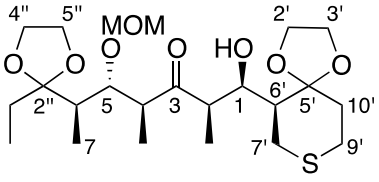
colorless solid, TLC R_f = 0.3 (10% ethyl acetate in hexanes).

^{1}H NMR (500 MHz, C_6D_6) δ 4.34 (1H, br d, J = 6 Hz, HC-3′), 3.56 (1H, br s, HO), 3.54-3.48 (4H, m, H_2C-4′, H_2C-5′), 3.43 (1H, br d, J = 10.5 Hz, HC-4), 3.18 (1H, br d, J = 10 Hz, HC-6), 2.29 (1H, br q, J = 7 Hz, HC-2′), 2.10 (1H, dq, J = 6, 7 Hz, HC-4′), 1.96 (1H, ddq, J = 10, 10.5, 6.5 Hz, HC-5), 1.88 (1H, m, J = 15, 7.5 Hz, HCC-2″), 1.73-1.80 (2H, m, HCC-2″, HCC-6), 1.45 (3H, d, J

= 7 Hz, H_3C-5′), 1.34 (3H, s, H_3CC-2), 1.29 (3H, d, *J* = 7 Hz, H_3C-1′), 1.19 (3H, s, H_3C-2), 1.01 (3H, d, *J* = 7 Hz, H_3CCC-6), 0.98 (3H, t, *J* = 7 Hz, H_3CCC-2″), 0.93 (3H, d, *J* = 7 Hz, H_3CCC-6), 0.66 (3H, d, *J* = 6.5 Hz, H_3CC-5).

^{13}C NMR (125 MHz, C_6D_6) δ 114.5 (s, C-2′), 98.8 (s, C-2), 81.8 (d, C-4), 78.6 (d, C-6), 70.0 (d, C-3′), 65.5 (t, C-4′), 65.2 (t, C-5′), 43.9 (d, C-4′), 37.7 (d, C-2′), 33.6 (d, C-5), 30.6 (d, CH_3C-2), 28.8 (d, CHC-6), 26.7 (t, CH_2C-2″), 20.8 (q, CH_3CC-6), 19.3 (q, CH_3C-2), 14.8 (q, CH_3CC-6), 13.1 (q, C-1′), 12.5 (q, C-5′), 11.9 (q, CH_3C-5), 7.7 (q, CH_3CC-2″); HRMS *m/z* calcd. for $C_{20}H_{38}O_5$+Na^+ 381.2611, found 381.2618 (ESI).

HRMS *m/z* calcd. for $C_{20}H_{38}O_5$+Na^+ 381.2611, found 381.2618 (ESI).



(84sss (Pg = MOM))

(1*R*,2*R*,4*S*,5*R*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-5-(methoxymethoxy)-2,4-dimethyl-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (84sss (Pg = MOM)).

From aldol (Li (*Z*)-enolate). See the preparation of **84ass** (Pg = MOM). From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of **65a** (33 mg, 0.11 mmol) with **29a** (47 mg, 0.25 mmol) according to the general procedure (using $TiCl(O\textit{i}\text{-}Pr)_3$; h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 12:1 mixture of **84sss** (Pg = MOM) and **84ass** (Pg = MOM), respectively. Fractionation of the crude by FCC (60% Et_2O in hexanes) gave **84ass** (Pg = MOM) (2 mg, 4%) the title compound (43 mg, 79%).

colorless viscous oil, TLC R_f = 0.3 (40% ethyl acetate in hexanes).

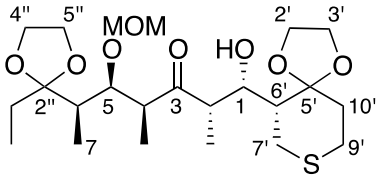
IR (DRIFT) ν_{max} 3513, 1708 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (1H, d, *J* = 6.5 Hz, HCO_2), 4.57 (1H, d, *J* = 6.5 Hz, HCO_2), 4.47 (1H, ddd, *J* = 2, 5, 5.5 Hz, HC-1), 4.05-3.91 (8H, m, H_2CO ×4), 3.77 (1H, dd, *J* = 2.5, 9 Hz, HC-5), 3.35 (1H, dq, *J* = 9, 7 Hz, HC-4), 3.33 (3H, s, *J* = Hz, H_3CO), 3.28 (1H, d, *J* = 2 Hz, HO), 3.02 (1H, dq, *J* = 5.5, 7 Hz, HC-2), 2.97 (1H, dd, *J* = 10, 13.5 Hz, HC-7'), 2.84 (1H, br d, *J* = 13.5

Hz, HC-7'), 2.73 (1H, ddd, J = 2.5, 10.5, 13.5 Hz, HC-9'), 2.60 (1H, br d, J = 13.5 Hz, HC-9'), 2.20 (1H, dq, J = 2.5, 7 Hz, HC-6), 2.12 (1H, ddd, J = 4, 5, 10 Hz, HC-6'), 2.08 (1H, ddd, J = 3, 6, 13.5 Hz, HC-10'), 1.82-1.67 (3H, m, HC-10', H_2CC-2''), 1.16 (3H, d, J = 7 Hz, H_3CC-2), 1.08 (3H, d, J = 7 Hz, H_3C-7), 1.05 (3H, d, J = 7 Hz, H_3CC-4), 0.89 (3H, t, J = 7.5 Hz, H_3CCC-2'').

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3 (s, C-3), 113.5 (s, C-2''), 109.9 (s, C-5'), 98.2 (t, OCH_2O), 83.3 (d, C-5), 67.9 (d, C-1), 65.6 (t, CH_2O), 65.2 (t, CH_2O), 64.6 (t, CH_2O), 64.5 (t, CH_2O), 56.5 (q, CH_3O), 50.7 (d, C-2), 47.0 (d, C-4), 46.5 (d, C-6'), 41.5 (d, C-6), 35.8 (t, C-10'), 28.9 (t, CH_2C-2''), 27.7 (t, C-7'), 26.7 (t, C-9'), 15.4 (q, CH_3C-4), 12.0 (q, C-7), 11.2 (q, CH_3C-2), 7.8 (q, CH_3CC-2'').

HRMS *m/z* calcd for $C_{23}H_{40}O_8S+Na^+$ 499.2336, found 499.2329 (ESI).



(81ass (Pg = MOM))

(1*S*,2*S*,4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-5-(methoxymethoxy)-2,4-dimethyl-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (81ass (Pg = MOM)).

From aldol (Li (*Z*)-enolate). Aldol reaction of **62a** (95 mg, 0.33 mmol) with **29a** (93 mg, 0.49 mmol according to the general procedure gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 6:3:1:2 mixture of **81ass** (Pg = MOM), **81sss** (Pg = MOM), an unidentified adduct,<NOTE: This is likely to be the **81aas** (Pg = MOM) diastereomer based on: i) the Li enolate of **62a** is a 10:1 mixture of *Z* and *E* diastereomers, respectively[124]; the *E* enolate reacts with *i*-PrCHO to give the *anti,anti* diastereomer predominantly[124]; iii) addition of enolates to aldehyde **29a** are known[108] to be highly Felkin selective) and **62a**, respectively. Fractionation of the crude product by FCC (60-80% Et_2O in hexanes) provided **81sss** (Pg = MOM) (42 mg, 27%) and the title compound (67 mg, 43%).

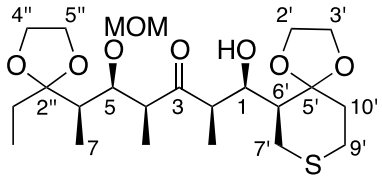
colorless oil, TLC R_f = 0.4 (60% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3518, 1705 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.67 (1H, d, *J* = 6.5 Hz, HCO_2), 4.56 (1H, d, *J* = 6.5 Hz, HCO_2), 4.27 (1H, ddd, *J* = 1.5, 3.5, 7 Hz, HC-1), 4.04-3.92 (9H, m, HC-5, H_2CO ×4), 3.053 (1H, dq, *J* = 7, 7 Hz, HC-2), 3.052 (1H, d, *J* = 1.5 Hz, HO), 2.97 (1H, dq, *J* = 5.5, 7 Hz, HC-4), 2.94 (1H, dd, *J* = 10.5, 14 Hz, HC-7'), 2.78-2.70 (2H, m, HC-7', HC-9'), 2.55 (1H, dddd, *J* = 2, 3.5, 5.5, 13.5 Hz, HC-9'), 2.07 (1H, ddd, *J* = 3, 5.5, 14 Hz, H_2C-10'), 1.88 (1H, dq, *J* = 3, 7 Hz, HC-6), 1.73-1.61 (3H, m, HC-10', H_2CC-2''), 1.87 (1H, ddd, *J* = 3.5, 4, 10.5 Hz, HC-6'), 1.16 (3H, d, *J* = 7 Hz, H_3CC-2), 1.11 (3H, d, *J* = 7 Hz, H_3CC-4), 0.93 (3H, d, *J* = 7 Hz, H_3C-7), 0.84 (3H, t, *J* = 7.5 Hz, H_3CCC-2'').

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.5 (s, C-3), 113.5 (s, C-2''), 109.9 (s, C-5'), 97.7 (t, OCH_2O), 76.6 (d, C-5), 69.6 (d, C-1), 65.30 (t, CH_2O), 65.28 (t, CH_2O), 64.8 (t, CH_2O), 64.5 (t, CH_2O), 56.5 (q, CH_3O), 51.4 (d, C-4), 48.8 (d, C-2), 47.2 (d, C-6'), 42.4 (d, C-6), 35.9 (t, C-10'), 27.1 (t, C-7', CH_2C-2''), 26.8 (t, C-9'), 12.5 (q, CH_3C-4), 12.4 (q, CH_3C-2), 10.3 (q, C-7), 7.7 (q, CH_3CC-2'').

HRMS *m/z* calcd for $C_{23}H_{40}O_8S+Na^+$ 499.2336, found 499.2355 (ESI).



(81sss (Pg = MOM))

(1*R*,2*R*,4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-5-(methoxymethoxy)-2,4-dimethyl-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (81sss (Pg = MOM)).

From aldol (Li (*Z*)-enolate). See the preparation of **81ass** (Pg = MOM). From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of **62a** (32 mg, 0.11 mmol) with **29a** (42 mg, 0.22 mmol) according to the general procedure (using $TiCl(O\textit{i}\text{-}Pr)_3$; 3 h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 77:15:8:15 mixture of **81ass** (Pg = MOM), **81ass** (Pg = MOM), and an unidentified aldol adduct (not present among the products from the (*Z*)-enol borinate below; possibly **81ssa** (Pg = MOM)), and **62a**, respectively. Fractionation of the crude product by FCC (40-70% Et_2O in hexanes) gave **62a** (2 mg, 6%) and the title compound (46 mg;

ca. 90% pure, ca 83%). From aldol (B (*Z*)-enolate). Aldol reaction of **62a** (30 mg, 0.10 mmol) with **29a** (40 mg, 0.21 mmol) according to the general procedure (enolization conditions: –78 °C, 2 h) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 6:1:1 mixture of **81sss** (Pg = MOM), **81ass** (Pg = MOM), and **62a**, respectively, along with two unidentified minor adducts (<5% each). Fractionation of the crude by FCC (40-70% ether in hexanes) gave recovered **62a** (3 mg, 10%) and the title compound (30 mg, 61%).

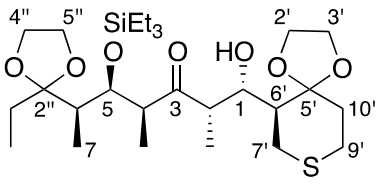
colorless oil, TLC R_f = 0.23 (60% ether in hexanes).

IR (DRIFT) ν_{max} 3514, 1693 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (1H, d, *J* = 6.5 Hz, HCO_2), 4.55 (1H, d, *J* = 6.5 Hz, HCO_2), 4.42 (1H, dd, *J* = 4.5, 5.5 Hz, HC-1), 4.02-3.92 (9H, m, HC-5, H_2CO ×4), 3.37 (1H, br s, HO), 3.36 (3H, s, H_3CO), 3.17 (1H, dq, *J* = 5.5, 7 Hz, HC-2), 3.05 (1H, dq, *J* = 4.5, 7 Hz, HC-4), 2.95 (1H, dd, *J* = 9.5, 14 Hz, HC-7'), 2.86 (1H, br dd, *J* = 14 Hz, HC-7'), 2.71 (1H, ddd, *J* = 2.5, 10, 13.5 Hz, HC-9'), 2.61 (1H, br d, *J* = 13.5 Hz, HC-9'), 2.09-2.02 (3H, m, HC-6, HC-6', HC-10'), 1.71-1.60 (3H, m, HC-10', H_2CC-2''), 1.17 (3H, d, *J* = 7 Hz, H_3CC-2), 1.08 (3H, d, *J* = 7 Hz, H_3CC-4), 0.92 (3H, d, *J* = 7 Hz, H_3C-7), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2'').

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.2 (s, C-3), 113.6 (s, C-2''), 109.7 (s, C-5'), 97.4 (t, OCH_2O), 77.2 (d, C-5), 68.2 (d, C-1), 65.2 (t, CH_2O), 65.1 (t, CH_2O), 64.6 (t, CH_2O), 64.4 (t, CH_2O), 56.4 (q, CH_3O), 49.9 (d, C-2), 49.0 (d, C-4), 46.6 (d, C-6'), 41.4 (d, C-6), 35.5 (t, C-10'), 27.8 (t, C-7'), 26.8 (t, CH_2C-2''), 26.7 (t, C-9'), 12.1 (q, CH_3C-4), 11.9 (q, CH_3C-2), 11.0 (q, C-7), 7.8 (q, CH_3CC-2'').

HRMS *m/z* calcd for $C_{23}H_{40}O_8S$+Na^+ 499.2336, found 499.2322 (ESI).



(81asa (Pg = TES))

(1*S*,2*S*,4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (81asa (Pg = TES)).

The minor product obtained from isomerization of **81sas** (Pg = TES) (see the preparation of **81ssa** (Pg = TES)).

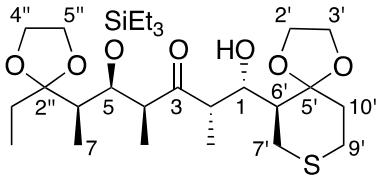
white solid, TLC R_f = 0.51 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3495, 2951 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.62 (1H, br d, *J* = 8 Hz, HC-1), 4.10 (1H, dd, *J* = 2, 6 Hz, HC-5), 4.04-3.98 (4H, m, H_2CO ×2), 3.96 (1H, br s, HO), 3.93-3.99 (4H, m, H_2CO ×2), 3.15 (1H, dq, *J* = 6, 7 Hz, HC-4), 2.87 (1H, br dd, *J* = 2, 14 Hz, HC-7'), 2.82-2.70 (3H, m, HC-2, H_2C-9'), 2.62 (1H, dd, *J* = 7, 14 Hz, H_2C-7'), 2.21 (1H, ddd, *J* = 4, 9, 13.5 Hz, HCC-10'), 1.97 (1H, ddd, *J* = 3, 7, 8 Hz, HC-6'), 1.88-1.82 (2H, m, HC-6, HC-10'), 1.71-1.59 (2H, m, H_2CC-2''), 1.08 (3H, d, *J* = 7 Hz, H_3CC-4), 1.03 (3H, d, *J* = 6.5 Hz, H_3CC-2), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.86 (3H, d, *J* = 7 Hz, H_3C-7), 0.84 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.64 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3 (s, C-3), 113.7 (s, C-2''), 110.8 (s, C-5'), 73.9 (d, C-5), 69.9 (d, C-1), 65.3 (t, CH_2O), 65.1 (t, CH_2O), 65.0 (t, CH_2O), 64.2 (t, CH_2O), 49.6 (d, C-4), 49.0 (d, C-2), 46.4 (d, C-6'), 42.6 (d, C-6), 34.6 (t, C-10'), 29.4 (t, C-7'), 27.3 (t, CH_2C-2''), 27.0 (t, C-9'), 14.1 (q, CH_3C-4), 10.0 (q, C-7), 7.5 (q ×2, CH_3C-2, CH_3CC-2''), 7.4 (q ×3, CH_3CSi), 5.7 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2934 (ESI).

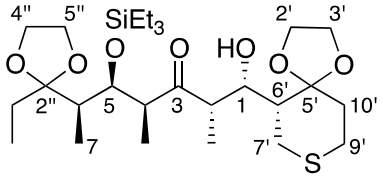


((+)-81asa (Pg = TES))

(1*S*,2*S*,4*S*,5*S*,6*R*)-(+)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((+)-81asa (Pg = TES)).

From isomerization with *i*-PrMgBr. Isomerization of (+)-**81sss** (Pg = TES) (50 mg, 0.09 mmol) according to the general procedure (*i*-PrMgBr, 3 d) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a single product (dr >19:1). Fractionation of the crude product by FCC (10% acetone in pentane) provided the title compound (29 mg, 58%) and a 4:1 mixture of (+)-**81asa** (Pg = TES) and (+)-**81ssa** (Pg = TES), respectively (8 mg, 13%). Fractionation of the mixture by PTLC (15% acetone in pentane) gave additional title compound (6 mg, 12%; total of 35 mg, 70%) ($[\alpha]_D$ +28.5, *c* 1.0, $CHCl_3$). NMR data for (+)-**81asa** (Pg = TES) closely matched those reported above for (±)-**81asa** (Pg = TES). From isomerizations with *i*-Pr_2Mg and then with *i*-PrMgBr. According to the general procedure for isomerizations with *i*-Pr_2Mg and then with *i*-PrMgBr, the crude product obtained from the reaction of **(+)-81sss** (22 mg, 0.04 mmol) indicated the presence of a 92:8 mixture of **(+)-81ssa** and **(+)-81asa**, respectively. Fractionation of the crude product by PTLC (40% ethyl acetate in hexanes) provided a 92:8 mixture of **(+)-81asa** and **(+)-81ssa** (14 mg, 64%), respectively.

colorless liquid, TLC R_f = 0.51 (20% ethyl acetate in hexanes).



(81ass (Pg = TES))

(1*S*,2*S*,4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (81ass (Pg = TES)).

From aldol (Li (*Z*)-enolate). Aldol reaction of **62b** (122 mg, 0.34 mmol) with **29a** (96 mg, 0.51 mmol) according to the general procedure gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 61:17:7:15 mixture of **81ass** (Pg = TES), **81sss** (Pg = TES), **81aas** (Pg = TES) (presumably from the Li (*E*)-enolate), and **62b**, respectively. Fractionation of the crude product by FCC (50-60% Et_2O in hexanes) provided **81sss** (Pg = TES) (29 mg, 16%) and the title compound as a 7:1 mixture with **81aas** (Pg = TES) (NOTE: This is likely to be the **81aas** (Pg = TES) diastereomer based on: i) the Li enolate of **62b** is a 10:1 mixture of *Z* and *E* diastereomers, respectively[124]; ii) the *E* enolate reacts with *i*-PrCHO to give the *anti*,*anti* diastereomer

predominantly[124]; iii) addition of enolates to aldehyde **29a** are known[108] to be highly Felkin selective) (118 mg, 64%).

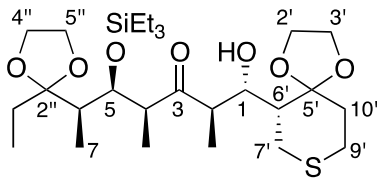
colorless liquid, TLC R_f = 0.3 (40% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3526, 1704 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.31 (1H, dd, *J* = 3, 6 Hz, HC-1), 4.21 (1H, dd, *J* = 4, 5 Hz, HC-5), 4.06-3.88 (8H, m, H_2CO ×4), 3.09 (1H, br s, HO), 3.02 (1H, dq, *J* = 6, 7 Hz, HC-2), 3.00-2.93 (2H, m, HC-4, HC-7'), 2.79-2.73 (2H, m, HC-7', HC-9'), 2.57 (1H, br d, *J* = 13.5 Hz, HC-9'), 2.08 (1H, ddd, *J* = 3, 5.5, 13.5 Hz, HC-10'), 1.91 (1H, ddd, *J* = 3, 3.5, 10.5 Hz, HC-6'), 1.82 (1H, dq, *J* = 3.5, 7 Hz, HC-6), 1.73-1.56 (3H, m, HC-10', H_2CC-2''), 1.16 (3H, d, *J* = 7 Hz, H_3CC-2), 1.08 (3H, d, *J* = 7 Hz, H_3CC-4), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.89 (3H, d, *J* = 7 Hz, H_3C-7), 0.84 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.63 (6H, ap q, *J* = 8 Hz, H_2CSi ×3), δ for minor isomer (partial data) 4.19 (1H, br d, *J* = 9 Hz), 4.13 (1H, dd, *J* = 2.5, 5 Hz), 2.83 (1H, br t, *J* = 13 Hz), 2.61 (1H, br d, *J* = 14 Hz), 2.51 (1H, br d, *J* = 13.5 Hz), 2.14 (1H, br dt, *J* = 13.5, 3.5 Hz), 2.02 (1H, br dd, *J* = 3.5, 12 Hz), 1.03 (3H, d, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4 (s, C-3), 113.7 (s, C-2''), 109.9 (s, C-5'), 71.5 (d, C-5), 69.2 (d, C-1), 65.3 (t, CH_2O), 65.1 (t, CH_2O), 64.7 (t, CH_2O), 64.5 (t, CH_2O), 52.2 (d, C-4), 48.7 (d, C-2), 47.3 (d, C-6'), 43.0 (d, C-6), 35.9 (t, C-10'), 27.5 (t, CH_2C-2''), 27.2 (t, C-7'), 26.8 (t, C-9'), 13.1 (q, CH_3C-4), 12.6 (q, CH_3C-2), 10.4 (q, C-7), 7.6 (q, CH_3CC-2''), 7.38 (q ×3, CH_3CSi), 5.66 (t ×3, CH_2Si), δ for minor isomer 218.2, 113.8, 110.4, 72.7, 72.6, 65.3, 65.1, 65.0, 64.4, 54.3, 48.6, 46.5, 41.8, 36.6, 27.0, 26.7, 25.8, 13.4, 12.9, 10.2, 7.5, 7.35, 5.64.

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2958 (ESI).



(81sas (Pg = TES))

(1*S*,2*R*,4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (81sas (Pg = TES)).

From aldol (B (*E*)-enolate). Aldol reaction of **62b** (300 mg, 0.84 mmol) with **29a** (473 mg, 2.5 mmol) according to the general procedure (enolization conditions A: *c*-Hex_2BCl, 2 equiv, 0 °C, 30 min) gave a crude product whose ^1H NMR spectrum indicated the presence of a single aldol adduct (>19:1 dr). Fractionation of the crude by FCC (30-40% Et_2O in hexanes) gave the title compound as a white solid (400 mg, 87%).

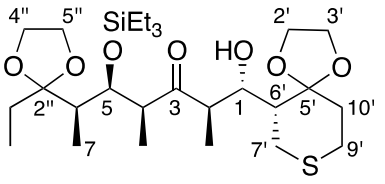
white solid, TLC R_f = 0.32 (40% ether in hexanes).

IR (DRIFT) ν_{max} 3524, 1709 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.28 (1H, dd, *J* = 4, 5 Hz, HC-5), 4.24 (1H, br d, *J* = 9.5 Hz, HC-1), 4.07-3.89 (8H, m, H_2CO ×4), 3.05 (1H, dd, *J* = 12, 14 Hz, HC-7'), 2.95 (1H, d, *J* = 2 Hz, HO), 2.94 (1H, dq, *J* = 5, 7 Hz, HC-4), 2.91 (1H, dq, *J* = 9.5, 7 Hz, HC-2), 2.82 (1H, ddd, *J* = 2.5, 13, 13.5 Hz, HC-9'), 2.59 (1H, ddd, *J* = 2, 3.5, 14 Hz, HC-7'), 2.51 (1H, dddd, *J* = 2, 3.5, 4, 13.5 Hz, HC-9'), 2.13 (1H, ddd, *J* = 2.5, 4, 13.5 Hz, HC-10'), 2.00 (1H, ddd, *J* = 1.5, 3.5, 11.5 Hz, HC-6'), 1.92 (1H, dq, *J* = 4, 7 Hz, HC-6), 1.72 (1H, ddd, *J* = 3.5, 13, 13.5 Hz, HC-10'), 1.72-1.58 (2H, m, H_2CC-2''), 1.12 (3H, d, *J* = 7 Hz, H_3CC-4), 0.96 (3H, d, *J* = 7 Hz, H_3CC-2), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.90 (3H, d, *J* = 7 Hz, H_3C-7), 0.83 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.64 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1 (s, C-3), 113.9 (s, C-2''), 110.3 (s, C-5'), 71.8 (d, C-1), 71.2 (d, C-5), 65.2 (t ×2, H_2CO), 64.8 (t, H_2CO), 64.4 (t, H_2CO), 53.5 (d, C-4), 47.1 (d, C-2), 46.5 (d, C-6'), 42.9 (d, C-6), 36.6 (t, C-10'), 27.4 (t, CH_2C-2''), 26.7 (t, C-9'), 25.9 (t, C-7'), 14.1 (q, CH_3C-4), 12.5 (q, CH_3C-2), 10.7 (q, C-7), 7.5 (q, CH_3CC-2''), 7.4 (q ×3, CH_3CSi), 5.6 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2925 (ESI).

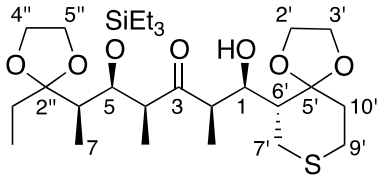


((–)-81sas (Pg = TES))

(1*S*,2*R*,4*S*,5*S*,6*R*)-(–)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((–)-81sas (Pg = TES)).

From aldol (B (*E*)-enolate). Aldol reaction of (+)-**62b** (>98% *ee*; 366 mg, 1.02 mmol) with **29a** (578 mg, 3.06 mmol) according to the general procedure (enolization conditions A: *c*-Hex_2BCl, 2 equiv, 0 °C, 30 min) gave a crude product whose ^1H NMR spectrum indicated the presence of a single aldol adduct (>19:1 dr). Fractionation of the crude by FCC (30-40% Et_2O in hexanes) gave the title compound as a white solid (531 mg, 95%) ($[\alpha]_D$ −16, *c* 1.0, $CHCl_3$). NMR data for (–)-**81sas** (Pg = TES) closely matched those reported above for (±)-**81sas** (Pg = TES).

white solid, TLC R_f = 0.32 (40% ether in hexanes).



(81ssa (Pg = TES))

(1*R*,2*R*,4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (81ssa (Pg = TES)).

Isomerization of **81sas** (Pg = TES) (60 mg, 0.11 mmol) according to the general procedure (*i*-PrMgBr, 3 d) gave a crude product whose ^1H NMR spectrum indicated the presence of a 1:1 mixture of **81ssa** (Pg = TES) and **81asa** (Pg = TES). Fractionation of the crude product by FCC (10% acetone in pentane) provided **81asa** (Pg = TES) (22 mg, 37%), a 1.1:1 mixture of **81asa** (Pg = TES) and **81ssa** (Pg = TES) (3 mg, 5%), and the title compound (23 mg, 38%).

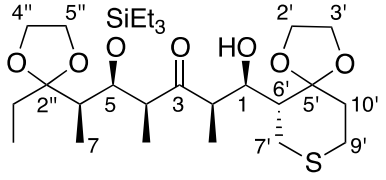
colorless liquid, TLC R_f = 0.52 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3499, 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (1H, br d, *J* = 8 Hz, HC-1), 4.32 (1H, dd, *J* = 3, 6.5 Hz, HC-5), 4.08-3.94 (4H, m, H_2CO ×2), 3.94-3.84 (4H, m, H_2CO ×2), 3.83 (1H, br s, HO), 3.13 (1H, dq, *J* = 6.5, 7 Hz, HC-4), 2.89 (1H, dd, *J* = 2.5, 14 Hz, HC-7'), 2.82-2.77 (2H, m, HC-2, HC-9'), 2.74-2.67 (1H, m, HC-9'), 2.59 (1H, dd, *J* = 7, 14 Hz, HC-7'), 2.19 (1H, ddd, *J* = 4, 9, 13.5 Hz, HC-10'), 1.95 (1H, ddd, *J* = 3, 7, 8.5 Hz, HC-6'), 1.92-1.82 (2H, m, HC-6, HC-10'), 1.74-160 (2H, m, H_2CC-2''), 1.11 (3H, d, *J* = 7 Hz, H_3CC-4), 1.06 (3H, d, *J* = 7 Hz, H_3CC-2), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.92 (3H, d, *J* = 7 Hz, H_3C-7), 0.84 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.65 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.5 (s, C-3), 113.7 (s, C-2''), 110.6 (s, C-5'), 72.1 (d, C-5), 69.6 (d, C-1), 65.2 (t, CH_2O), 65.1 (t, CH_2O), 65.0 (t, CH_2O), 64.3 (t, CH_2O), 49.5 (d, C-4), 46.3 (d, C-6'), 46.2 (d, C-2), 43.1 (d, C-6), 34.4 (t, C-10'), 29.4 (t, C-7'), 27.4 (t, CH_2C-2''), 27.0 (t, C-9'), 14.7 (q, CH_3C-4), 10.0 (q, C-7), 7.9 (q, CH_3C-2), 7.4 (q ×4, CH_3CSI, CH_3CC_2''), 5.8 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2944 (ESI).



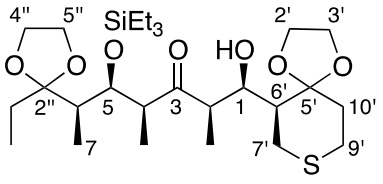
((+)-81ssa (Pg = TES))

(1*R*,2*R*,4*S*,5*S*,6*R*)-(+)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((+)-81ssa (Pg = TES)).

From isomerization with *i*-PrMgBr. Isomerization of **(–)-81sas** (Pg = TES) (64 mg, 0.12 mmol) according to the general procedure (*i*-PrMgBr, 3 d) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 6:1 mixture of **81ssa** (Pg = TES) and **81asa** (Pg = TES). Fractionation of the crude product by FCC (10% acetone in pentane) provided a 6:1 mixture of **81asa** (Pg = TES) and **81ssa** (Pg = TES), respectively (8 mg, 13%), and the title compound (46 mg, 72%) ($[\alpha]_D$ +18, *c* 1.0, $CHCl_3$). NMR data for (+)-**81ssa** (Pg = TES) closely matched those reported above for (±)-**81ssa** (Pg = TES). From isomerizations with *i*-Pr_2Mg and then with *i*-PrMgBr. According to the general procedure for isomerizations with *i*-Pr_2Mg and then with *i*-

PrMgBr, the crude product obtained from the reaction of **(−)-81sas** (25 mg, 0.05 mmol) indicated the presence of a 90:10 mixture of **(+)-81ssa** and **(+)-81asa**, respectively. Fractionation of the crude product by PTLC (40% ethyl acetate in hexanes) provided a 90:10 mixture of **(+)-81ssa** and **(+)-81asa** (16 mg, 64%), respectively.

colorless liquid, TLC R_f = 0.52 (20% ethyl acetate in hexanes).



(81sss (Pg = TES))

(1*R*,2*R*,4*S*,5*S*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (81sss (Pg = TES)).

From aldol (Li (*Z*)-enolate). See the preparation of **81ass** (Pg = TES). From aldol (B (*Z*)-enolate). Aldol reaction of **62b** (31 mg, 0.087 mmol) with **29a** (32 mg, 0.17 mmol) according to the general procedure (enolization conditions: –78 °C, 4 h) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 21:2:1.3:1:8 mixture of **81sss** (Pg = TES), **81ass** (Pg = TES), **81ssa** (Pg = TES), **81sas** (Pg = TES), and **62b**, respectively. Fractionation of the crude by FCC (10-20% acetone in hexanes) gave **62b** (5 mg, 16%) and the titled compound (21 mg, 44%). From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of **62b** (32 mg, 0.090 mmol) with **29a** (34 mg, 0.18 mmol) according to the general procedure (using TiCl(O*i*-Pr)$_3$; 18 h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 5:1:2 mixture of **81sss** (Pg = TES), **81ssa** (Pg = TES), and **62b**, respectively. Fractionation of the crude product by FCC (40-70% Et_2O in hexanes) gave the **62b** (3 mg, 9%) and the title compound (30 mg, 61%).

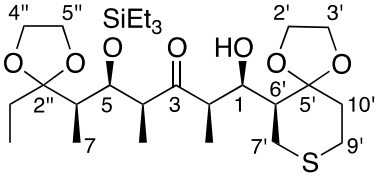
colorless oil, TLC R_f = 0.21 (40% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3520, 1692 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (1H, ddd, *J* = 1.5, 3.5, 5.5 Hz, HC-1), 4.12 (1H, dd, *J* = 3, 4.5 Hz, HC-5), 4.02-3.89 (8H, m, H_2CO ×4), 3.34 (1H, d, *J* = 1.5 Hz, HO), 3.09 (1H, dq, *J* = 5.5, 7 Hz, HC-2), 3.00-2.94 (2H, m, HC-4, HC-7'), 2.84 (1H, br d, *J* = 13.5 Hz, HC-7'), 2.70 (1H, ddd, *J* = 2.5, 10, 13.5 Hz, HC-9'), 2.61 (1H, br d, *J* = 13.5 Hz, HC-9'), 2.06-1.97 (2H, m, HC-6'; HC-10'), 1.89 (1H, dq, *J* = 3, 7 Hz, HC-6), 1.74-1.54 (3H, m, HC-10', H_2CC-2''), 1.18 (3H, d, *J* = 7 Hz, H_3CC-2), 1.06 (3H, d, *J* = 7 Hz, H_3CC-4), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.87 (3H, d, *J* = 7 Hz, H_3C-7), 0.85 (3H, ap t, *J* = 7.5 Hz, H_3CCC-2''), 0.64 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.5 (s, C-3), 113.7 (s, C-2''), 109.7 (s, C-5'), 72.5 (d, C-5), 68.5 (d, C-1), 65.2 (t, CH_2O), 65.1 (t, CH_2O), 64.6 (t, CH_2O), 64.4 (t, CH_2O), 51.5 (d, C-4), 49.6 (d, C-2), 46.7 (d, C-6'), 41.9 (d, C-6), 35.6 (t, C-10'), 27.8 (t, C-7'), 27.0 (t, CH_2C-2''), 26.7 (t, C-9'), 13.3 (q, CH_3C-4), 11.8 (q, CH_3C-2), 10.7 (q, C-7), 7.5 (q, CH_3CC-2''), 7.3 (q ×3, CH_3CSi), 5.5 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2938, found 569.2948 (ESI).



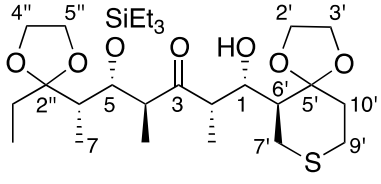
((+)-81sss (Pg = TES))

(1*R*,2*R*,4*S*,5*S*,6*R*)-(+)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((+)-81sss (Pg = TES)).

From aldol (B (*Z*)-enolate). Aldol reaction of (+)-**62b** (>98% *ee*; 60 mg, 0.17 mmol) with **29a** (95 mg, 0.50 mmol) according to the general procedure (enolization conditions: –78 °C, 4 h) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 12.8:1.5:1:1.3:2.1 mixture of **81sss** (Pg = TES), **81ass** (Pg = TES), **81ssa** (Pg = TES), **81sas** (Pg = TES), and **62b** (ca. 90% conversion), respectively. Fractionation of the crude product by FCC (30-50% Et_2O in hexanes) gave a 1:1 mixture of **81ass** (Pg = TES) and **81ssa** (Pg = TES) (10 mg, 11%), a 50:36:14 mixture of **81sss** (Pg = TES), **81sas** (Pg = TES), and **81ass** (Pg = TES) (20 mg, 21%), and the title compound (52 mg, 56%). From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of (+)-**62b** (>98% *ee*;

50 mg, 0.14 mmol) with **29a** (80 mg, 0.42 mmol) according to the general procedure (using $TiCl(O\textit{i}\text{-}Pr)_3$; 16 h aldol reaction time) gave a crude product whose ^1H NMR spectrum indicated the presence of a 10:1:0.5:0.8:2:7 mixture of **81sss** (Pg = TES), **81ass** (Pg = TES), **81ssa** (Pg = TES), **81sas** (Pg = TES), **81aas** (Pg = TES) (tentative), and **62b** (ca. 85% conversion), respectively. Fractionation of the crude product by FCC (30-50% Et_2O in hexanes) provided the title compound (50 mg, 66%) ($[\alpha]_D$ +48, *c* 1.0, $CHCl_3$).

colorless oil, TLC R_f = 0.21 (40% ether in hexanes). NMR data for (+)-**81sss** (Pg = TES) closely matched those reported above for (±)-**81sss** (Pg = TES).



(82asa (Pg = TES))

(1*S*,2*S*,4*S*,5*R*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (82asa (Pg = TES)).

The minor product obtained from isomerization of **82sas** (Pg = TES) (see the preparation of **82ssa** (Pg = TES)).

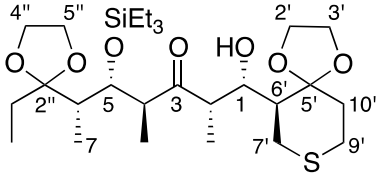
colorless solid, TLC R_f = 0.40 (15% acetone in pentane).

IR (DRIFT) ν_{max} 3502, 1712 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.70 (1H, dd, *J* = 2, 9 Hz, HC-1), 4.26 (1H, br d, *J* = 5 Hz, HC-5), 4.05-3.96 (5H, m, HO, H_2CO ×2), 3.88-3.72 (4H, m, H_2CO ×2), 3.24 (1H, dq, *J* = 5, 6.5 Hz, HC-4), 2.92 (1H, dd, *J* = 2.5, 14 Hz, HC-7'), 2.88-2.79 (2H, m, HC-2, HC-9'), 2.74-2.68 (1H, m, HC-9'), 2.63 (1H, dd, *J* = 6.5, 14 Hz, HC-7'), 2.21 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10'), 1.96 (1H, ddd, *J* = 3, 6.5, 9 Hz, HC-6'), 1.87 (1H, ddd, *J* = 3.5, 7, 13.5 Hz, HC-10'), 1.85 (1H, br q, *J* = 7 Hz, HC-6), 1.67 (1H, dq, *J* = 14, 7.5 Hz, HCC-2''), 1.59 (1H, dq, *J* = 14, 7.5 Hz, HCC-2''), 1.05 (3H, d, *J* = 6.5 Hz, H_3CC-4), 1.03 (3H, d, *J* = 7 Hz, H_3CC-2), 0.98 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.92 (3H, d, *J* = 7 Hz, H_3C-7), 0.82 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.71-0.62 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.5 (s, C-3), 114.0 (s, C-2''), 110.7 (s, C-5'), 70.4 (d ×2, C-1, C-5), 65.2 (t, CH_2O), 65.0 (t, CH_2O), 64.8 (t, CH_2O), 64.2 (t, CH_2O), 50.8 (d, C-4), 47.7 (d, C-2), 46.2 (d, C-6'), 40.5 (d, C-6), 34.4 (t, C-10'), 29.2 (t, C-7'), 27.0 (t, C-9'), 26.0 (t, CH_2C-2''), 10.8 (q, C-7), 10.6 (q, CH_3C-4), 7.3 (q ×3, CH_3CSi), 7.2 (q, CH_3CC-2''), 7.1 (q, CH_3C-2), 5.5 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2928 (ESI).

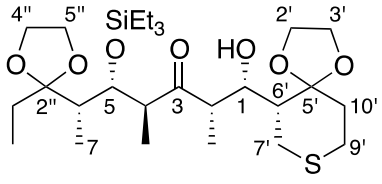


((+)-82asa (Pg = TES))

(1*S*,2*S*,4*S*,5*R*,6*S*)-(+)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((+)-82asa (Pg = TES)).

Isomerization of (+)-**82sss** (Pg = TES) (70 mg, 0.13 mmol) according to the general procedure (*i*-PrMgBr, 3 d) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a single product (dr >19:1). Fractionation of the crude product by FCC (10% acetone in pentane) provided the title compound (57 mg, 81%) ($[\alpha]_D$ +39, *c* 1.0, $CHCl_3$). NMR data for (+)-**82asa** (Pg = TES) closely matched those reported above for (±)-**82asa** (Pg = TES).

.



(82ass (Pg = TES))

(1*S*,2*S*,4*S*,5*R*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (82ass (Pg = TES)).

From aldol (Li (*Z*)-enolate). Aldol reaction of **63b** (70 mg, 0.19 mmol) with **29a** (55 mg, 0.29 mmol) according to the general procedure gave a crude product whose ^{1}H NMR spectrum

indicated the presence of a 8:2:3:2 mixture of **82ass** (Pg = TES), **82sss** (Pg = TES), **82sas** (Pg = TES), and **63b**, respectively. Fractionation of the crude product by FCC (40-50% Et_2O in hexanes) provided **82sss** (Pg = TES) (14 mg, 13%) and a 3:1 mixture of the **82ass** (Pg = TES) and **82sas** (Pg = TES), respectively (77 mg, 72%), that was further fractionated by FCC (10-20% acetone in hexanes) to afford 1.5:1 mixture of **82ass** (Pg = TES) and **82sas** (Pg = TES), respectively (47 mg, 44%), and the title compound (27 mg, 25%).

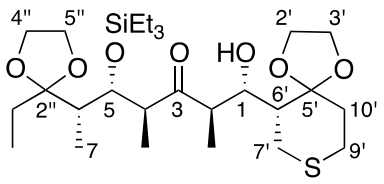
colorless liquid, TLC R_f = 0.31 (50% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3524, 1704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (1H, ddd, *J* = 2, 3.5, 5.5 Hz, HC-1), 4.26 (1H, dd, *J* = 1.5, 5 Hz, HC-5), 4.07-3.78 (8H, m, H_2CO ×4), 3.05 (1H, dq, *J* = 5.5, 7 Hz, HC-2), 3.02 (2H, m, *J* = 5, 7 Hz, HC-4), 2.99 (1H, d, *J* = 1.5 Hz, HO), 2.97 (1H, dd, *J* = 10, 14 Hz, HC-7'), 2.80-2.71 (2H, m, HC-7', HC-9'), 2.63-2.57 (1H, m, HC-9'), 2.08 (1H, ddd, *J* = 3, 6, 13.5 Hz, HC-10'), 1.94 (1H, ddd, *J* = 3.5, 4, 10 Hz, HC-6'), 1.92 (1H, dq, *J* = 1.5, 7 Hz, HC-6), 1.73 (1H, ddd, *J* = 3.5, 10.5, 14 Hz, HC-10'), 1.69 (1H, dq, *J* = 14.5, 7.5 Hz, HCC-2''), 1.63 (1H, dq, *J* = 14.5, 7.5 Hz, HCC-2''), 1.16 (3H, d, *J* = 7 Hz, H_3CC-2), 1.05 (3H, d, *J* = 7 Hz, H_3CC-4), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.93 (3H, d, *J* = 7 Hz, H_3C-7), 0.83 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.64 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5 (s, C-3), 114.0 (s, C-2''), 109.8 (s, C-5'), 69.9 (d, C-5), 69.8 (d, C-1), 65.2 (t, CH_2O), 65.0 (t, CH_2O), 64.7 (t, CH_2O), 64.5 (t, CH_2O), 54.4 (d, C-4), 49.9 (d, C-2), 47.0 (d, C-6'), 40.8 (d, C-6), 35.7 (t, C-10'), 27.5 (t, C-7'), 26.8 (t, C-9'), 26.4 (t, CH_2C-2''), 11.6 (q ×2, CH_3C-2, CH_3C-4), 10.8 (q, C-7), 7.29 (q ×3, CH_3CH_2Si), 7.24 (q, CH_3CC-2''), 5.5 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2944.



(82sas (Pg = TES))

(1*S*,2*R*,4*S*,5*R*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (82sas (Pg = TES)).

From aldol (B (*E*)-enolate). Aldol reaction of **63b** (46 mg, 0.13 mmol) with **29a** (75 mg, 0.39 mmol) according to the general procedure (enolization conditions A: *c*-Hex_2BCl, 2 equiv, 0 °C, 1 h) gave a crude product whose ^1H NMR spectrum indicated the presence of a 5:1 mixture of a single aldol adduct (>19:1 dr) and **63b**, respectively. Careful fractionation of the crude product by FCC (30-40% Et_2O in hexanes) gave recovered **63b** (6 mg, 13%) and the title compound (56 mg, 80%).

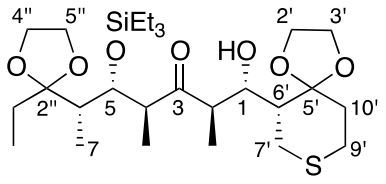
colorless oil, TLC R_f = 0.35 (40% ether in hexanes).

IR (DRIFT) ν_{max} 3523, 1711 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.27-4.24 (2H, m, HC-1, HC-5), 4.08-3.83 (8H, m, H_2CO ×4), 3.061 (1H, dd, *J* = 11.5, 14 Hz, HC-7'), 3.060 (1H, d, *J* = 2 Hz, HO), 2.98 (1H, dq, *J* = 4.5, 7 Hz, HC-4), 2.854 (1H, dq, *J* = 9.5, 7 Hz, HC-2), 2.850 (1H, ddd, *J* = 3, 12, 13.5 Hz, HC-9'), 2.59 (1H, ddd, *J* = 2.5, 3.5, 14 Hz, HC-7'), 2.51 (1H, dddd, *J* = 2.5, 3.5, 4, 13.5 Hz, HC-9'), 2.13 (1H, ddd, *J* = 3, 4, 14 Hz, HC-10'), 2.04 (1H, ddd, *J* = 2, 3.5, 11.5 Hz, HC-6'), 2.02 (1H, dq, *J* = 2, 7 Hz, HC-6), 1.74 (1H, ddd, *J* = 3.5, 13, 13 Hz, HC-10'), 1.70-1.57 (2H, m, H_2CC-2''), 1.11 (3H, d, *J* = 7 Hz, H_3CC-4), 1.02 (3H, d, *J* = 7 Hz, H_3CC-2), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.92 (3H, d, *J* = 7 Hz, H_3C-7), 0.82 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.63 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (150 MHz, $CDCl_3$) δ 216.0 (s, C-3), 114.0 (s, C-2''), 110.1 (s, C-5'), 71.1 (d, C-1), 70.2 (d, C-5), 65.1 (t, CH_2O), 65.0 (t, CH_2O), 64.9 (t, CH_2O), 64.6 (t, CH_2O), 53.3 (d, C-4), 48.6 (d, C-2), 46.8 (d, C-6'), 40.8 (d, C-6), 37.0 (t, C-10'), 26.8 (t, C-9'), 26.3 (t, CH_2C-2''), 26.1 (t, C-7'), 14.1 (q, CH_3C-2), 12.0 (q, CH_3C-4), 10.9 (q, C-7), 7.3 (q ×3, CH_3CSi), 7.2 (q, CH_3CC-2''), 5.5 (t ×3, CH_2Si).

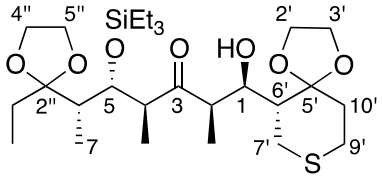
HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2944 (ESI).



((+)-82sas (Pg = TES))

(1*S*,2*R*,4*S*,5*R*,6*S*)-(+)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((+)-82sas (Pg = TES)).

From aldol (B (*E*)-enolate). Aldol reaction of (+)-**63b** (>98% *ee*; 85 mg, 0.24 mmol) with **29a** (135 mg, 0.71 mmol) according to the general procedure (enolization conditions A: *c*-Hex_2BCl, 2 equiv, 0 °C, 1 h) gave a crude product whose ^1H NMR spectrum indicated the presence of a 6:1 mixture of a single aldol adduct (>19:1 dr) and **63b**, respectively. Fractionation of the crude product by FCC (30-40% Et_2O in hexanes) gave recovered (+)-**63b** (9 mg, 11%) and the title compound (107 mg, 83%) ($[\alpha]_D$ +11, *c* 1.0, $CHCl_3$). NMR data for (+)-**82sas** (Pg = TES) closely matched those reported above for (±)-**82sas** (Pg = TES).



(82ssa (Pg = TES))

(1*R*,2*R*,4*S*,5*R*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (82ssa (Pg = TES)).

Isomerization of **82sas** (Pg = TES) (62 mg, 0.11 mmol) according to the general procedure (*i*-PrMgBr, 3 d) gave a crude product whose ^1H NMR spectrum indicated the presence of a 1.1:1 mixture of **82ssa** (Pg = TES) and **82asa** (Pg = TES), respectively. Fractionation of the crude product by FCC (10% acetone in pentane) provided **82asa** (Pg = TES) (17 mg, 27%), a 2:1 mixture of **82asa** (Pg = TES) and **82ssa** (Pg = TES) (10 mg, 16%), and the title compound (25 mg, 40%).

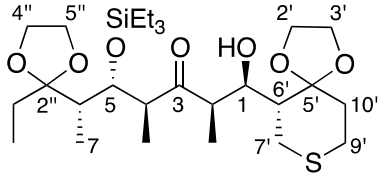
colorless liquid, TLC R_f = 0.41 (15% acetone in pentane).

IR (DRIFT) ν_{max} 3497, 1701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (1H, ddd, *J* = 1.5, 2.5, 8.5 Hz, HC-1), 4.24 (1H, dd, *J* = 1.5, 5 Hz, HC-5), 4.06-3.95 (4H, m, H_2CO ×2), 3.93-3.82 (4H, m, H_2CO ×2), 3.84 (1H, dd, *J* = 1.5, 1.5 Hz, HO), 2.60 (1H, dd, *J* = 8. 13.5 Hz, HC-7'), 3.12 (1H, dq, *J* = 5, 7 Hz, HC-4), 2.77 (1H, dd, *J* = 3, 13.5 Hz, HC-7'), 2.76-2.68 (2H, m, H_2C-9'), 2.62 (1H, ddq, *J* = 1.5, 2.5, 7 Hz, HC-2), 2.18 (1H, ddd, *J* = 5.5, 6, 13.5 Hz, HC-10'), 2.03-1.99 (2H, m, HC-6, HC-6'), 1.83 (1H, ddd, *J* = 5.5, 6.5, 13.5 Hz, HC-10'), 1.73-1.55 (2H, m, H_2CC-2''), 1.21 (3H, d, *J* = 7 Hz, H_3CC-2), 1.04 (3H, d, *J* = 7 Hz, H_3CC-4), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.92 (3H, d, *J* = 7 Hz, H_3C-7), 0.82 (3H, t, *J* = 7.5 Hz, H_3CCH_2C-2''), 0.62 (6H, ap q, *J* = 8 Hz, H_2CSi ×3) .

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2 (s, C-3), 113.9 (s, C-2''), 110.7 (s, C-5'), 70.5 (d, C-5), 70.4 (d, C-1), 65.3 (t, CH_2O), 64.9 (t ×2, CH_2O), 64.2 (t, CH_2O), 50.8 (d, C-4), 47.7 (d, C-2), 46.9 (d, C-6'), 40.4 (d, C-6), 34.9 (t, C-10'), 29.2 (t, C-7'), 26.8 (t, C-9'), 26.3 (t, CH_2C-2''), 11.9 (q, CH_3C-4), 10.6 (q, C-7), 8.9 (q, CH_3C-2), 7.29 (q ×3, CH_3CSi), 7.24 (q, CH_3CC-2''), 5.5 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2929 (ESI).

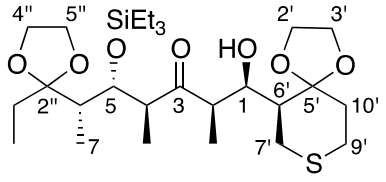


((+)-82ssa (Pg = TES))

(1*R*,2*R*,4*S*,5*R*,6*S*)-(+)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((+)-82ssa (Pg = TES)).

From isomerization with *i*-PrMgBr. Isomerization of (+)-**82sas** (Pg = TES) (50 mg, 0.090 mmol) according to the general procedure (*i*-PrMgBr, 3 d) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 19:1 mixture of **82ssa** (Pg = TES) and **82asa** (Pg = TES), respectively. Fractionation of the crude product by FCC (10% acetone in pentane) provided the title compound (39 mg, 78%) and 1.4:1 mixture of **82ssa** (Pg = TES) and **82asa** (Pg = TES) (7 mg, 14%). Fractionation of the latter mixture by PTLC (15% acetone in pentane) gave (+)-**82asa** (Pg = TES) (2 mg, 4%) and additional title compound (4 mg, 8%; total of 43 mg, 86%) ($[\alpha]_D$ +68, *c* 1.0, $CHCl_3$). NMR data for (+)-**82ssa** (Pg = TES) closely matched those reported

above for (±)-**82ssa** (Pg = TES). From isomerizations with *i*-Pr_2Mg and then with *i*-PrMgBr. According to the general procedure for isomerizations with *i*-Pr_2Mg and then with *i*-PrMgBr, the crude product obtained from the reaction of **(+)-82sas** (20 mg, 0.04 mmol) indicated the presence of a 93:7 mixture of **(+)-82ssa** and **(+)-82asa**, respectively. Fractionation of the crude product by PTLC (40% ethyl acetate in hexanes) provided a 93:7 mixture of **(+)-82ssa** and **(+)-82asa** (16 mg, 64%), respectively.



(82sss (Pg = TES))

(1*R*,2*R*,4*S*,5*R*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (82sss (Pg = TES)).

From aldol (Li (*Z*)-enolate). See the preparation of **82ass** (Pg = TES). From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of **63b** (41 mg, 0.11 mmol) with **29a** (65 mg, 0.34 mmol) according to the general procedure (using $TiCl_2(O$*i*$-Pr)_2$; 16 h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 1.4:0.13:0.1:0.14:0.22 mixture of **82sss** (Pg = TES), **82ass** (Pg = TES), **82ssa** (Pg = TES), **82sas** (Pg = TES), and **63b**, respectively. Fractionation of the crude product by FCC (20-40% Et_2O in hexanes) provided the title compound (44 mg, 70%).

colorless oil, TLC R_f = 0.65 (60% Et_2O in hexanes).

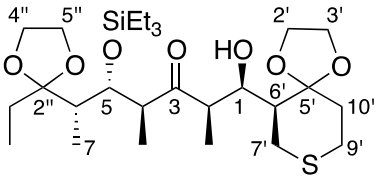
IR (DRIFT) ν_{max} 3520, 1695 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (1H, ddd, *J* = 1.5, 3, 7 Hz, HC-1), 4.20 (1H, dd, *J* = 1.5, 3.5 Hz, HC-5), 4.03-3.80 (8H, m, H_2CO ×4), 3.61 (1H, d, *J* = 1.5 Hz, HO), 3.27 (1H, dq, *J* = 3, 7 Hz, HC-2), 3.04 (1H, dq, *J* = 3.5, 7 Hz, HC-4), 3.01 (1H, dd, *J* = 3.5, 13.5 Hz, HC-7'), 2.96 (1H, dd, *J* = 7, 13.5 Hz, HC-7'), 2.77 (1H, ddd, *J* = 3, 9, 13.5 Hz, HC-9'), 2.60 (1H, ddd, *J* = 3.5, 7.5, 13.5 Hz, HC-9'), 2.07 (1H, ddd, *J* = 3.5, 9, 13.5 Hz, HC-10'), 2.00 (1H, ddd, *J* = 3.5, 7, 7 Hz, HC-6'), 1.92 (1H, dq, *J* = 1.5, 7 Hz, HC-6), 1.69 (1H, ddd, *J* = 3, 7.5, 13.5 Hz, HC-10'), 1.68 (1H, dq, *J* = 14.5,

7.5 Hz, HCC-2"), 1.56 (1H, dq, J = 14.5, 7.5 Hz, HCC-2"), 1.17 (3H, d, J = 7 Hz, H_3CC-2), 1.02 (3H, d, J = 7 Hz, H_3CC-4), 0.98 (9H, t, J = 8 Hz, H_3CCSi ×3), 0.91 (3H, d, J = 7 Hz, H_3C-7), 0.81 (3H, t, J = 7.5 Hz, H_3CCC-2"), 0.65 (6H, ap q, J = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3 (s, C-3), 113.9 (s, C-2"), 109.3 (s, C-5'), 69.9 (d, C-5), 67.5 (d, C-1), 65.4 (t, CH_2O), 65.1 (t, CH_2O), 64.8 (t, CH_2O), 64.1 (t, CH_2O), 53.1 (d, C-4), 48.3 (d, C-2), 46.0 (d, C-6'), 40.4 (d, C-6), 34.2 (t, C-10'), 28.7 (t, C-7'), 26.8 (t, C-9'), 25.6 (t, CH_2C-2"), 11.0 (q, C-7), 10.9 (q, CH_3C-2), 10.2 (q, CH_3C-4), 7.2 (q ×3, CH_3CSi), 6.9 (q, CH_3CC-2"), 5.5 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2927 (ESI).

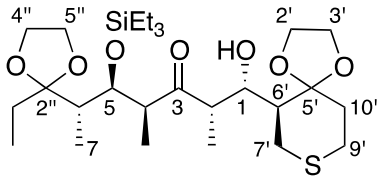


((+)-82sss (Pg = TES))

(1*R*,2*R*,4*S*,5*R*,6*S*)-(+)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((+)-82sss (Pg = TES)).

From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of (+)-**63b** (>98% *ee*; 50 mg, 0.14 mmol) with **29a** (80 mg, 0.42 mmol) according to the general procedure (using $TiCl_2(Oi\text{-}Pr)_2$; 16 h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 0.8:0.12:0.1:0.15:0.18 mixture of **82sss** (Pg = TES), **82ass** (Pg = TES), **82ssa** (Pg = TES), **82sas** (Pg = TES), and **63b**, respectively. Fractionation of the crude product by FCC (20-40% Et_2O in hexanes) provided the title compound (46 mg, 60%). NMR data for (+)-**82sss** (Pg = TES) closely matched those reported above for (±)-**82sss** (Pg = TES) ($[\alpha]_D$ +59, *c* 1.0, $CHCl_3$).

colorless oil, TLC R_f = 0.65 (60% Et_2O in hexanes).



(83asa (Pg = TES))

(1*S*,2*S*,4*S*,5*S*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (83asa (Pg = TES)).

The minor product obtained from isomerization of **83sas** (Pg = TES) (see the preparation of **83ssa** (Pg = TES)).

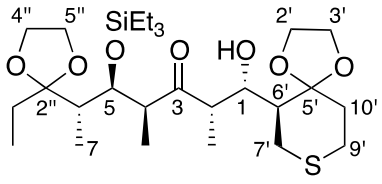
colorless liquid, TLC R_f = 0.51 (10% isopropanol in hexanes).

IR (DRIFT) ν_{max} 3497, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (1H, br d, *J* = 8.5 Hz, HC-1), 4.19 (1H, dd, *J* = 2.5, 7 Hz, HC-5), 4.06-3.95 (4H, m, H_2CO ×2), 3.92 (1H, br s, HO), 3.92-3.80 (4H, m, H_2CO 2), 3.30 (1H, dq, *J* = 7, 7 Hz, HC-4), 2.90-2.87 (2H, m, HC-2, HC-7'), 2.80 (1H, ddd, *J* = 3.5, 9, 13.5 Hz, HC-9'), 2.72 (1H, ddd, *J* = 3.5, 7, 13.5 Hz, HC-9'), 2.61 (1H, dd, *J* = 7, 14 Hz, HC-7'), 2.20 (1H, ddd, *J* = 3.5, 9, 13.5 Hz, HC-10'), 2.01 (1H, dq, *J* = 2.5, 7 Hz, HC-6), 1.97 (1H, ddd, *J* = 3, 7, 7 Hz, HC-6'), 1.85 (1H, ddd, *J* = 3.5, 7, 13.5 Hz, HC-10'), 1.60 (2H, ap q, *J* = 7.5 Hz, H_2CC-2"), 1.14 (3H, d, *J* = 7 Hz, H_3CC-4), 1.03 (3H, d, *J* = 7 Hz, H_3CC-2), 1.00 (3H, d, *J* = 7 Hz, H_3C-7), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.85 (3H, t, *J* = 7.5 Hz, H_3CCC-2"), 0.62 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.7 (s, C-3), 113.2 (s, C-2"), 110.7 (s, C-5'), 73.2 (d, C-5), 69.6 (d, C-1), 65.7 (t, CH_2O), 65.0 (t, CH_2O), 64.7 (t, CH_2O), 64.2 (t, CH_2O), 48.1 (d, C-2), 46.4 (d, C-6'), 45.9 (d, C-4), 45.7 (d, C-6), 34.6 (t, C-10'), 29.5 (t, C-7'), 28.9 (t, CH_2C-2"), 27.0 (t, C-9'), 15.8 (q, CH_3C-4), 10.4 (q, C-7), 8.3 (q, H_3CCC-2"), 7.5 (q, H_3CC-2), 7.2 (q ×3, CH_3CSi), 5.4 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2955 (ESI).

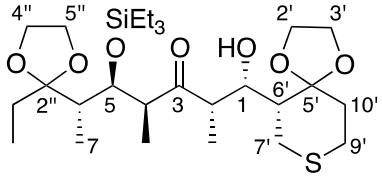


((–)-83asa (Pg = TES))

(1*S*,2*S*,4*S*,5*S*,6*S*)-(–)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((–)-83asa (Pg = TES)).

Isomerization of (−)-**83sss** (Pg = TES) (81% *ee*; 39 mg, 0.07 mmol) according to the general procedure (*i*-PrMgBr, 6 d) gave a crude product whose ^{1}H NMR spectrum indicated the presence of 3:1 mixture of **83asa** (Pg = TES) and **83ssa** (Pg = TES). Fractionation of the crude product by FCC (15% acetone in pentane) provided the title compound 2.8:1 mixture of **83asa** (Pg = TES) and **83ssa** (Pg = TES) (29 mg, 74%). Fractionation of the above mixture by PTLC (10% *i*-PrOH in hexanes) provided (+)-**83ssa** (Pg = TES) (7 mg, 18%) and the title compound (21 mg, 54%) ([α]$_D$ −4, *c* 1.0, $CHCl_3$). NMR data for (–)-**83asa** (Pg = TES) closely matched those reported above for (±)-**83asa** (Pg = TES).

colorless liquid, TLC R_f = 0.51 (10% isopropanol in hexanes).



(83ass (Pg = TES))

(1*S*,2*S*,4*S*,5*S*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (83ass (Pg = TES)).

From aldol (Li (*Z*)-enolate). Aldol reaction of **64b** (62 mg, 0.17 mmol) with **29a** (49 mg, 0.26 mmol) according to the general procedure gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 5:5:1:4.7 mixture of **83ass** (Pg = TES), **83sss** (Pg = TES), an unidentified adduct (NOTE: This is likely to be the **83aas** (Pg = TES) diastereomer based on: i) the Li enolate of **64b** is a 15:1 mixture of *Z* and *E* diastereomers, respectively[124]; ii) the *E* enolate reacts with *i*-PrCHO to give the *anti,anti* diastereomer predominantly[124]; iii) addition of enolates

to aldehyde **CHO** are known[108] to be highly Felkin selective), and **64b**, respectively. Fractionation of the crude product by FCC (40-50% Et_2O in hexanes) provided **64b** (16 mg, 26%), **83sss** (Pg = TES) (22 mg, 23%), a 1.8:1.5:1 mixture of **83sss** (Pg = TES), **83ass** (Pg = TES), and **83aas** (Pg = TES), respectively (16 mg, 17%), and the title compound (25 mg, 27%).

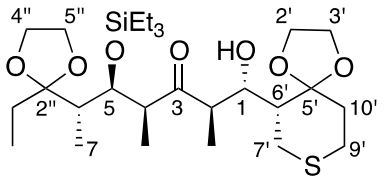
colorless liquid, TLC R_f = 0.34 (50% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3524, 1704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (1H, dd, *J* = 3, 3.5 Hz, HC-5), 4.33 (1H, ddd, *J* = 1.5, 4, 6.5 Hz, HC-1), 4.07-3.82 (8H, m, H_2CO ×4), 3.22 (1H, dq, *J* = 3.5, 7 Hz, HC-4), 3.17 (1H, br s, HO), 3.09 (1H, dq, *J* = 6.5, 7 Hz, HC-2), 2.97 (1H, dd, *J* = 10.5, 14 Hz, HC-7'), 2.81-2.73 (2H, m, HC-7', HC-9'), 2.62-2.54 (1H, m, HC-9'), 2.12-2.03 (2H, m, HC-10', HC-6), 1.92 (1H, ddd, *J* = 3.5, 3.5, 10.5 Hz, HC-6'), 1.69 (1H, ddd, *J* = 3.5, 11, 13.5 Hz, HC-10'), 1.64-1.51 (2H, m, H_2CC-2''), 1.16 (3H, d, *J* = 7 Hz, H_3CC-2), 1.14 (3H, d, *J* = 7.5 Hz, H_3CC-4), 0.99 (3H, d, *J* = 7 Hz, H_3C-7), 0.95 (9H, t , *J* = 8 Hz, H_3CCSi ×3), 0.87 (3H, ap t, *J* = 7.5 Hz, H_3CCC-2'), 0.68-0.51 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4 (s, C-3), 113.2 (s, C-2''), 109.9 (s, C-5'), 69.3 (d, C-1), 68.5 (d, C-5), 65.8 (t, CH_2O), 64.8 (t, CH_2O), 64.7 (t, CH_2O), 64.5 (t, CH_2O), 47.3 (d, C-6'), 47.2 (d, C-4), 47.1 (d, C-2), 46.0 (d, C-6), 36.0 (t, C-10'), 29.1 (t, CH_2C-2''), 27.3 (t, C-7'), 26.8 (t, C-9'), 13.3 (q, CH_3C-4), 13.1 (q, CH_3C-2), 9.6 (q, C-7), 8.2 (q, CH_3CC-2''), 7.2 (q ×3, CH_3CSi), 5.3 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2938, found 569.2917 (ESI).



(83sas (Pg = TES))

(1*S*,2*R*,4*S*,5*S*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (83sas (Pg = TES)).

From aldol (B (*E*)-enolate). Aldol reaction of **64b** (92 mg, 0.26 mmol) with **29a** (150 mg, 0.76 mmol) according to the general procedure (enolization conditions A: *c*-Hex_2BCl, 2 equiv, 0 °C, 2 h) gave a crude product whose ^1H NMR spectrum indicated the presence of a single aldol adduct (>19:1 dr). Fractionation of the crude product by FCC (30-40% Et_2O in hexanes) gave the title compound (125 mg, 89%).

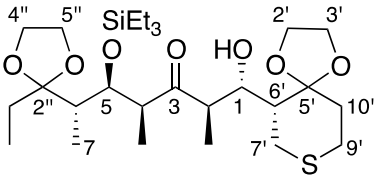
white solid, TLC R_f = 0.32 (40% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3526, 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (1H, dd, *J* = 2.5, 3 Hz, HC-5), 4.29 (1H, ddd, *J* = 1.5, 2, 9.5 Hz, HC-1), 4.07-3.82 (8H, m, H_2CO ×4), 3.09 (1H, dq, *J* = 2.5, 7.5 Hz, HC-4), 3.04 (1H, dd, *J* = 11.5, 14 Hz, HC-7'), 2.97 (1H, dq, *J* = 9.5, 7 Hz, HC-2), 2.91 (1H, d, *J* = 2 Hz, HO), 2.81 (1H, ddd, *J* = 2.5, 12.5, 13.5 Hz, HC-9'), 2.60 (1H, ddd, *J* = 2.5, 3.5, 14 Hz, HC-7'), 2.51 (1H, dddd, *J* = 2.5, 3.5, 4, 13.5 Hz, HC-9'), 2.13 (1H, ddd, *J* = 2.5, 4.5, 14 Hz, HC-10'), 2.04 (1H, dq, *J* = 3, 7 Hz, HC-6), 2.01 (1H, ddd, *J* = 1.5, 3.5, 11.5 Hz, HC-6'), 1.72 (1H, ddd, *J* = 3.5, 12.5, 14 Hz, H_2C-10'), 1.62 (2H, ap q, *J* = 7.5 Hz, H_2CC-2''), 1.18 (3H, d, *J* = 7.5 Hz, H_3CC-4), 1.00 (3H, d, *J* = 7 Hz, H_3C-7), 0.96 (3H, d, *J* = 7 Hz, H_3CC-2), 0.93 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.86 (3H, ap t, *J* = 7.5 Hz, H_3CCC-2''), 0.67-0.55 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9 (s, C-3), 113.4 (s, C-2''), 110.3 (s, C-5'), 71.7 (d, C-1), 68.4 (d, C-5), 65.7 (t, CH_2O), 64.9 (t, CH_2O), 64.8 (t, CH_2O), 64.4 (t, CH_2O), 50.1 (d, C-4), 46.5 (d, C-6'), 46.02 (d, C-6), 45.96 (d, C-2), 36.6 (t, C-10'), 28.9 (t, CH_2C-2''), 26.7 (t, C-9'), 26.0 (t, C-7'), 14.5 (q, CH_3C-2), 12.2 (q, CH_3C-4), 10.3 (q, C-7), 8.2 (q, CH_3CC-2''), 7.2 (q ×3, CH_3CSi), 5.3 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2953 (ESI).

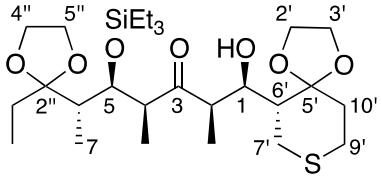


((–)-83sas (Pg = TES))

(1*S*,2*R*,4*S*,5*S*,6*S*)-(–)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((–)-83sas (Pg = TES)).

From aldol (B (*E*)-enolate). Aldol reaction of (–)-**64b** (81% *ee*; 50 mg, 0.14 mmol) with **29a** (80 mg, 0.42 mmol) according to the general procedure (enolization conditions A: *c*-Hex_2BCl, 2 equiv, 0 °C, 2 h) gave a crude product whose ^1H NMR spectrum indicated the presence of a single aldol adduct (>19:1 dr). Fractionation of the crude product by FCC (30-40% Et_2O in hexanes) gave the title compound (62 mg, 81%) ($[\alpha]_D$ −18, *c* 1.0, $CHCl_3$). NMR data for (–)-**83sas** (Pg = TES) closely matched those reported above for (±)-**83sas** (Pg = TES).

colorless viscous oil, TLC R_f = 0.32 (40% ether in hexanes).



(83ssa (Pg = TES))

(1*R*,2*R*,4*S*,5*S*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (83ssa (Pg = TES)).

Isomerization of **83sas** (Pg = TES) (100 mg, 0.18 mmol) according to the general procedure (*i*-PrMgBr, 6 d) gave a crude product whose ^1H NMR spectrum indicated the presence of a 2:1 mixture of **83ssa** (Pg = TES) and **83asa** (Pg = TES), respectively. Fractionation of the crude product by FCC (10-15% acetone in pentane) provided a 1.9:1 mixture of **83ssa** (Pg = TES) and **83asa** (Pg = TES) (69 mg, 69%). Fractionation of the above mixture by FCC (5-10% *i*-PrOH in hexanes) gave **83asa** (Pg = TES) (21 mg, 21%) and the title compound (45 mg, 45%) .

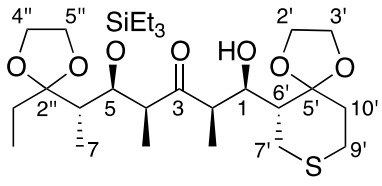
white solid, TLC R_f = 0.53 (10% isopropanol in hexanes).

IR (DRIFT) ν_{max} 3500, 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (1H, br d, *J* = 8 Hz, HC-1), 4.48 (1H, dd, *J* = 3, 4 Hz, HC-5), 4.04-3.81 (8H, m, H_2CO ×4), 3.78 (1H, br s, HO), 3.40 (1H, dq, *J* = 4, 7.5 Hz, HC-4), 2.90 (1H, dd, *J* = 3, 14 Hz, HC-7'), 2.85-2.79 (2H, m, HC-2, HC-9'), 2.72-2.66 (1H, m, HC-9'), 2.59 (1H, ddd, *J* = 1, 6.5, 14 Hz, HC-7'), 2.24 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10'), 2.04 (1H, dq, *J* = 3, 7 Hz, HC-6), 1.93 (1H, ddd, *J* = 3, 6.5, 8.5 Hz, HC-6'), 1.83 (1H, ddd, *J* = 3.5, 6.5, 13.5 Hz, HC-10'), 1.67-1.55 (2H, m, H_2CC-2''), 1.14 (3H, d, *J* = 7.5 Hz, H_3CC-4), 1.08 (3H, d, *J* = 7 Hz, H_3CC-2), 1.01 (3H, d, *J* = 7 Hz, H_3C-7), 0.94 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.85 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.69-0.56 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9 (s, C-3), 113.6 (s, C-2''), 110.7 (s, C-5'), 70.1 (d, C-5), 69.7 (d, C-1), 65.9 (t, H_2CO), 64.9 (t 2, H_2CO), 64.2 (t, H_2CO), 46.2 (d, C-6'), 45.7 (d, C-6), 45.2 (d, C-4), 45.0 (d, C-2), 34.2 (t, C-10'), 29.4 (t, C-7'), 29.3 (t, CH_2C-2''), 27.0 (t, C-9'), 14.3 (q, CH_3C-4), 10.3 (q, C-7), 8.1 (q 2, CH_3C-2, H_3CCC-2''), 7.3 (q 3, CH_3CSi), 5.3 (t 3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2964 (ESI).

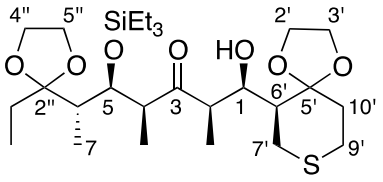


((+)-83ssa (Pg = TES))

(1*R*,2*R*,4*S*,5*S*,6*S*)-(+)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((+)-83ssa (Pg = TES)).

Isomerization of (–)-**83sas** (Pg = TES) (81% *ee*; 60 mg, 0.11 mmol) according to the general procedure (*i*-PrMgBr, 6 d) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 5:1 mixture of **83ssa** (Pg = TES) and **83asa** (Pg = TES), respectively. Fractionation of the crude product by FCC (15% acetone in pentane) provided the title compound (16 mg, 27%) and a 2.4:1 mixture of **83ssa** (Pg = TES) and **83asa** (Pg = TES), respectively (26 mg, 43%), by ^{1}H NMR. Fractionation of the latter mixture by PTLC (10% *i*-PrOH in hexanes) provided (−)-**83asa**

(Pg = TES) (11 mg, 12%) and the title compound (18 mg, 30%; total yield = 34 mg, 57%) ($[\alpha]_D$ +6, *c* 1.0, $CHCl_3$). NMR data for (+)-**83ssa** (Pg = TES) closely matched those reported above for (±)-**83ssa** (Pg = TES).



(83sss (Pg = TES))

(1*R*,2*R*,4*S*,5*S*,6*S*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (83sss (Pg = TES)).

From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of **64b** (50 mg, 0.14 mmol) with **29a** (79 mg, 0.42 mmol) according to the general procedure (using $TiCl_2(Oi\text{-}Pr)_2$; 16 h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a mixture of 1:0.1:0.06:0.04:0.3 mixture of **83sss** (Pg = TES), **83ssa** (Pg = TES), **83sas** (Pg = TES), **83aas** (Pg = TES) (tentatively identified), and **64b**, respectively. Fractionation of the crude product by FCC (30-50% Et_2O in hexanes) provided the title compound (49 mg, 64%).

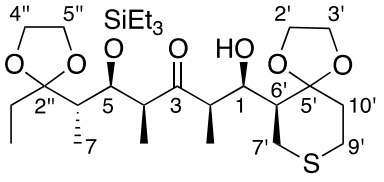
colorless oil, TLC R_f = 0.65 (60% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3520, 1703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (1H, ap t, *J* = 3, 3.5 Hz, HC-5), 4.39 (1H, ddd, *J* = 2, 5, 5.5 Hz, HC-1), 4.04-3.83 (8H, m, H_2CO ×4), 3.24 (1H, d, *J* = 2 Hz, HO), 3.16 (1H, dq, *J* = 3.5, 7 Hz, HC-4), 3.12 (1H, dq, *J* = 5.5, 7 Hz, HC-2), 2.97 (1H, dd, *J* = 9, 14 Hz, HC-7'), 2.85 (1H, dd, *J* = 1.5, 3.5, 14 Hz, HC-7'), 2.72 (1H, ddd, *J* = 3.5, 10, 13.5 Hz, HC-9'), 2.63 (1H, dddd, *J* = 1.5, 3.5, 6.5,13.5 Hz, HC-9'), 2.09 (1H, dq, *J* = 3, 7 Hz, HC-6), 2.07 (1H, ddd, *J* = 3.5, 6.5, 13.5 Hz, HC-10'), 1.96 (1H, ddd, *J* = 3.5, 5, 9 Hz, HC-6'), 1.70 (1H, ddd, *J* = 3.5, 10, 13.5 Hz, HC-10'), 1.65-1.53 (2H, m, H_2CC-2"), 1.16 (6H, ap d, *J* = 7 Hz, H_3CC-2, H_3CC-4), 1.00 (3H, t, *J* = 7 Hz, H_3C-7), 0.94 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.88 (3H, t, *J* = 7.5 Hz, H_3CCC-2"), 0.61 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3 (s, C-3), 113.2 (s, C-2''), 109.7 (s, C-5'), 68.8 (d, C-1), 68.7 (d, C-5), 65.8 (t, CH_2O), 64.8 (t, CH_2O), 64.7 (t, CH_2O), 64.5 (t, CH_2O), 47.74 (d, C-4), 47.66 (d, C-2), 46.8 (d, C-6'), 46.0 (d, C-6), 35.6 (t, C-10'), 28.9 (t, CH_2C-2''), 27.9 (t, C-7'), 26.8 (t, C-9'), 13.4 (q, CH_3C-4), 12.0 (q, CH_3C-2), 9.4 (q, C-7), 8.3 (q, CH_3CC-2''), 7.2 (q ×3, CH_3CSi), 5.3 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2938, found 569.2961 (ESI).

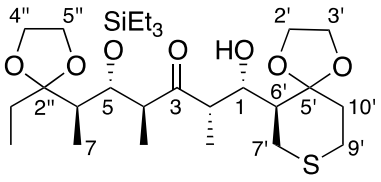


((–)-83sss (Pg = TES))

(1*R*,2*R*,4*S*,5*S*,6*S*)-(–)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((–)-83sss (Pg = TES)).

From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of (–)-**64b** (81% *ee*; 50 mg, 0.14 mmol) with **29a** (79 mg, 0.42 mmol) according to the general procedure (using $TiCl_2(O$*i*$-Pr)_2$; 16 h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a mixture of 1:0.16:0.08:0.12:0.16 mixture of **83sss** (Pg = TES), **83ssa** (Pg = TES), **83sas** (Pg = TES), **83aas** (Pg = TES) (tentatively identified), and **64b**, respectively. Fractionation of the crude product by FCC (30-50% Et_2O in hexanes) provided the title compound (54 mg, 71%) ($[\alpha]_D$ −13, *c* 1.0, $CHCl_3$). NMR data for (–)-**83sss** (Pg = TES) closely matched those reported above for (±)-**83sss** (Pg = TES).

colorless viscous oil, TLC R_f = 0.65 (60% Et_2O in hexanes).



(84asa (Pg = TES))

(1*S*,2*S*,4*S*,5*R*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (84asa (Pg = TES)).

Isomerization of **84sas** (Pg = TES) (60 mg, 0.11 mmol) according to the general procedure (*i*-PrMgBr, 6 d) gave a crude product whose ^{1}H NMR spectrum suggested the presence of a 1.4:1 mixture of **84asa** (Pg = TES) and **84ssa** (Pg = TES), respectively. Fractionation of the crude product by FCC (10% acetone in pentane) provided **84asa** (Pg = TES) (23 mg, 38%), a 1.6:1 mixture of **84ssa** (Pg = TES) and **84asa** (Pg = TES) (6 mg, 10%), and the title compound (16 mg, 26%).

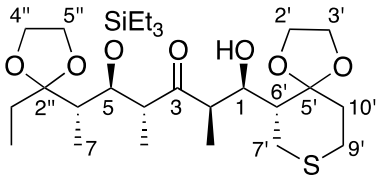
colorless solid, TLC R_f = 0.3 (60% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3501, 1714 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.75 (1H, br d, *J* = 8.5 Hz, HC-1), 4.04-3.90 (9H, m, HC-5, H_2CO ×4), 3.89 (1H, br s, HO), 3.44 (1H, dq, *J* = 8.5, 7 Hz, HC-4), 2.92 (1H, dd, *J* = 2.5, 14 Hz, HC-7'), 2.83 (1H, ddd, *J* = 3, 10, 13.5 Hz, HC-9'), 2.77-2.68 (2H, m, HC-2, HC-9'), 2.58 (1H, dd, *J* = 6.5, 14 Hz, HC-7'), 2.23 (1H, ddd, *J* = 3.5, 10, 13.5 Hz, H_2C-10'), 2.06 (1H, dq, *J* = 2, 7 Hz, HC-6), 1.95 (1H, ddd, *J* = 3, 6.5, 9 Hz, HC-6'), 1.87 (1H, ddd, *J* = 3, 6.5, 13.5 Hz, H_2C-10'), 1.75 (1H, dq, *J* = 14.5, 7.5 Hz, H_2CC-2''), 1.69 (1H, dq, *J* = 14.5, 7.5 Hz, H_2CC-2''), 1.055 (3H, d, *J* = 7 Hz, H_3C-7), 1.049 (3H, d, *J* = 7 Hz, H_3CC-4), 1.03 (3H, d, *J* = 6.5 Hz, H_3CC-2), 0.91 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.88 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.61-0.50 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0 (s, C-3), 113.6 (s, C-2''), 110.7 (s, C-5'), 77.6 (d, C-5), 69.5 (d, C-1), 65.6 (t ×2, CH_2O), 65.1 (t, CH_2O), 64.2 (t, CH_2O), 50.0 (d, C-2), 46.1 (d, C-6'), 45.7 (d, C-4), 44.3 (d, C-6), 34.4 (t, C-10'), 29.5 (t, C-7'), 29.3 (t, CH_2C-2''), 27.0 (t, C-9'), 14.9 (q, CH_3C-4), 11.7 (q, C-7), 8.0 (q, CH_3CC-2''), 7.2 (q ×3, CH_3CSi), 6.9 (q, CH_3C-2), 5.3 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2929 (ESI).

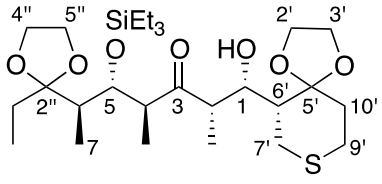


((–)-84asa (Pg = TES))

(1*R*,2*R*,4*R*,5*S*,6*S*)-(–)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((–)-84asa (Pg = TES)).

Isomerization of (–)-**84sss** (Pg = TES) (30 mg, 0.055 mmol) according to the general procedure (*i*-PrMgBr, 3 d) gave a crude product whose ^{1}H NMR spectrum suggested the presence of a 4.6:1 mixture **84asa** (Pg = TES) and **84ssa** (Pg = TES), respectively. Fractionation of the crude product by FCC (40-60% Et_2O in hexanes) gave a 1.5:1 mixture **84ssa** (Pg = TES) and **84asa** (Pg = TES), respectively (7 mg, 23%), and the title compound (17 mg, 57%) ($[\alpha]_D$ −29, *c* 0.5, $CHCl_3$). NMR data for (–)-**84asa** (Pg = TES) closely matched those reported above for (±)-**84asa** (Pg = TES).

brown liquid, TLC R_f = 0.3 (60% Et_2O in hexanes).



(84ass (Pg = TES))

(1*S*,2*S*,4*S*,5*R*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-5-(methoxymethoxy)-2,4-dimethyl-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (84ass (Pg = TES)).

From aldol (Li (*Z*)-enolate). Aldol reaction of **65b** (38 mg, 0.11 mmol) with **29a** (52 mg, 0.28 mmol) according to the general procedure gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 6:1 mixture of **84ass** (Pg = TES) and **84sss** (Pg = TES), respectively, along with **65b**. Fractionation of the crude by PTLC (70% Et_2O in hexanes, developed twice) furnished recovered **65b** (5 mg, 13%), **84sss** (Pg = TES) (5 mg, 9%), and the title compound (9 mg, 67%).

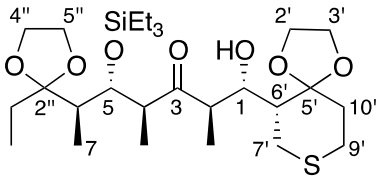
colorless oil, TLC R_f = 0.55 (70% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3524, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (1H, ddd, *J* = 2, 4.5, 6 Hz, HC-1), 4.08 (1H, dd, *J* = 2, 9 Hz, HC-5), 4.06-3.91 (8H, m, H_2CO ×4), 3.18 (1H, dq, *J* = 9, 7 Hz, HC-4), 3.10 (1H, d, *J* = 2 Hz, HO), 2.98 (1H, dq, *J* = 6, 7 Hz, HC-2), 2.96 (1H, dd, *J* = 10, 14 Hz, HC-7'), 2.82 (1H, ddd, *J* = 2, 3, 14 Hz, HC-7'), 2.75 (1H, ddd, *J* = 3, 10, 13.5 Hz, HC-9'), 2.59 (1H, br d, *J* = 13.5 Hz, HC-9'), 2.06 (1H, ddd, *J* = 3, 6, 13.5 Hz, HC-10'), 2.03 (1H, dq, *J* = 2, 7 Hz, HC-6), 1.98 (1H, ddd, *J* = 3, 4.5, 10 Hz, HC-6'), 1.80-1.65 (3H, m, HC-10', H_2CC-2''), 1.16 (3H, d, *J* = 7 Hz, H_3CC-2), 1.06 (9H, d, *J* = 7 Hz, H_3C-7), 1.01 (3H, d, *J* = 7 Hz, H_3CC-4), 0.93 (3H, t, *J* = 8 Hz, H_3CCSi ×3), 0.88 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.59 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9 (s, C-3), 113.7 (s, C-2''), 109.8 (s, C-5'), 75.4 (d, C-5), 68.8 (d, C-1), 65.5 (t, CH_2O), 65.3 (t, CH_2O), 64.64 (t, CH_2O), 64.61 (t, CH_2O), 49.6 (d, C-2), 49.3 (d, C-4), 47.3 (d, C-6'), 44.1 (d, C-6), 35.8 (t, C-10'), 29.1 (t, CH_2C-2''), 27.7 (t, C-7'), 26.8 (t, C-9'), 14.9 (q, CH_3C-4), 12.0 (q, C-7), 10.9 (q, CH_3C-2), 7.9 (q, CH_3CC-2''), 7.3 (q ×3, CH_3CSi), 5.3 (t ×3, H_2CSi).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2947 (ESI).



(84sas (Pg = TES))

(1*S*,2*R*,4*S*,5*R*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-3-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (84sas (Pg = TES)).

From aldol (B (*E*)-enolate). Aldol reaction of **65b** (90 mg, 0.25 mmol) with **29a** (188 mg, 1.00 mmol) according to the general procedure (enolization conditions B: *c*-Hex_2BCl, 2.2 equiv) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 6:1 mixture of a single adduct (>19:1 dr) and **65b**, respectively. Fractionation of the crude by FCC (30-40% Et_2O in hexanes) gave recovered **65b** (16 mg, 18%) and the title compound (112 mg, 82%).

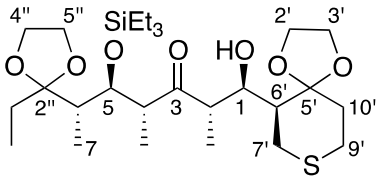
colorless liquid, TLC R_f = 0.33 (40% ether in hexanes).

IR (DRIFT) ν_{max} 3528, 1713 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (1H, br d, *J* = 9.5 Hz, HC-1), 4.12 (1H, dd, *J* = 3, 7 Hz, HC-5), 4.08-3.89 (8H, m, H_2CO ×4), 3.17 (1H, dq, *J* = 7, 7 Hz, HC-4), 3.12 (1H, d, *J* = 2 Hz, HO), 3.09 (1H, dd, *J* = 12, 14 Hz, HC-7'), 2.89 (1H, dq, *J* = 9.5, 7 Hz, HC-2), 2.87 (1H, ddd, *J* = 2.5, 13, 13.5 Hz, HC-9'), 2.59 (1H, ddd, *J* = 2.5, 3, 14 Hz, HC-7'), 2.50 (1H, dddd, *J* = 2.5, 3.5, 4, 13.5 Hz, HC-9'), 2.12 (1H, ddd, *J* = 2.5, 4, 13.5 Hz, HC-10'), 2.07-2.02 (2H, m, HC-6, HC-6'), 1.74 (1H, ddd, *J* = 3.5, 13, 13.5 Hz, H_2C-10'), 1.74-1.58 (2H, m, H_2CC-2''), 1.10 (3H, d, *J* = 7 Hz, H_3CC-4), 1.01 (3H, d, *J* = 7 Hz, H_3CC-2), 1.00 (3H, d, *J* = 7 Hz, H_3C-7), 0.94 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.63 (6H, m, H_2CSi ×3).

^{13}C NMR (150 MHz, $CDCl_3$) δ 217.7 (s, C-3), 113.5 (s, C-2''), 110.1 (s, C-5'), 76.0 (d, C-5), 71.4 (d, C-1), 65.5 (t, CH_2O), 65.1 (t, CH_2O), 65.0 (t, CH_2O), 64.6 (t, CH_2O), 50.0 (d, C-4), 48.5 (d, C-2), 47.0 (d, C-6'), 44.8 (d, C-6), 37.3 (t, C-10'), 29.1 (t, CH_2C-2''), 26.8 (t, C-9'), 26.0 (t, C-7'), 14.9 (q, CH_3C-4), 14.0 (q, CH_3C-2), 11.3 (q, C-7), 8.0 (q, CH_3CC-2''), 7.2 (q ×3, CH_3CSi), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2946 (ESI).



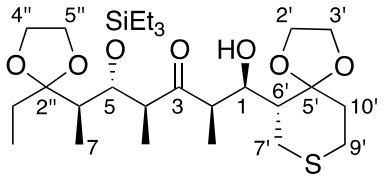
((+)-84sas (Pg = TES))

(1*R*,2*S*,4*R*,5*S*,6*S*)-(+)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-3-(triethylsilyl)oxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((+)-84sas (Pg = TES)).

From aldol (B (*E*)-enolate). Aldol reaction of (−)-**65b** (81% *ee*; 45 mg, 0.12 mmol) with **29a** (95 mg, 0.50 mmol) according to the general procedure (enolization conditions B: *c*-Hex_2BCl, 2.5 equiv) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 4:1 mixture of a single adduct (>19:1 dr) and **65b**, respectively. Fractionation of the crude by FCC

(30-40% Et_2O in hexanes) gave recovered (−)-**65b** (7 mg, 16%) and the title compound (52 mg, 76%) ($[\alpha]_D$ +7, *c* 1.0, $CHCl_3$). NMR data for (+)-**84sas** (Pg = TES) closely matched those reported above for (±)-**84sas** (Pg = TES).

colorless liquid, TLC R_f = 0.33 (40% ether in hexanes).



(84ssa (Pg = TES))

(1*R*,2*R*,4*S*,5*R*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (84ssa (Pg = TES)).

The minor product obtained from isomerization of **84sas** (Pg = TES) (see the preparation of **84asa** (Pg = TES)).

colorless liquid, TLC R_f = 0.3 (50% Et_2O in hexanes).

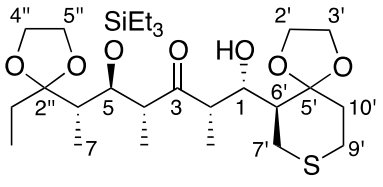
IR (DRIFT) ν_{max} 3508, 1700 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.51 (1H, br d, *J* = 9 Hz, HC-1), 4.07 (1H, dd, *J* = 2.5, 8.5 Hz, HC-5), 4.07-3.90 (8H, m, H_2CO ×4), 3.79 (1H, br s, HO), 3.36 (1H, dq, *J* = 8.5, 7 Hz, HC-4), 2.75-2.70 (3H, m, HC-7', H_2C-9'), 2.57 (1H, dd, *J* = 8, 13.5 Hz, H_2C-7'), 2.55 (1H, br q, *J* = 7 Hz, HC-2), 2.17 (1H, ddd, *J* = 4, 7.5, 13.5 Hz, H_2C-10'), 2.04 (1H, dq, *J* = 2.5, 7 Hz, HC-6), 2.00 (1H, ddd, *J* = 3, 8, 9 Hz, HC-6'), 1.82 (1H, ddd, *J* = 3.5, 8, 13.5 Hz, H_2C-10'), 1.76 (1H, dq, *J* = 14.5, 7.5 Hz, HCC-2''), 1.69 (1H, dq, *J* = 14.5, 7.5 Hz, HCC-2''), 1.21 (3H, d, *J* = 7 Hz, H_3CC-2), 1.04 (3H, d, *J* = 7 Hz, H_3C-7), 1.01 (3H, d, *J* = 7 Hz, H_3CC-4), 0.92 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.58 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.7 (s, C-3), 113.6 (s, C-2''), 110.6 (s, C-5'), 76.7 (d, C-5), 69.8 (d, C-1), 65.5 (t, CH_2O), 65.2 (t, CH_2O), 65.0 (t, CH_2O), 64.2 (t, CH_2O), 48.0 (d, C-2), 47.3 (d, C-

6'), 46.5 (d, C-4), 44.3 (d, C-6), 35.1 (t, C-10'), 29.1 (t ×2, C-7', CH_2C-2"), 26.8 (t, C-9'), 14.8 (q, CH_3C-4), 11.8 (q, C-7), 8.6 (q, CH_3C-2), 7.9 (q, CH_3CC-2"), 7.3 (q ×3, CH_3CSi), 5.3 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2939, found 569.2947 (ESI).

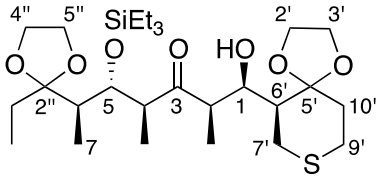


((–)-84ssa (Pg = TES))

(1*S*,2*S*,4*R*,5*S*,6*S*)-(–)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-5-(triethylsilyl)oxy-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((–)-84ssa (Pg = TES)).

Isomerization of (+)-**84sas** (Pg = TES) (30 mg, 0.055 mmol) according to the general procedure (*i*-PrMgBr, 6 d) gave a crude product whose ^{1}H NMR spectrum indicated the presence of 6:1 mixture **84ssa** (Pg = TES) and **84asa** (Pg = TES), respectively. Fractionation of the crude product by FCC (10% acetone in pentane) gave (–)-**84asa** (Pg = TES) (7 mg, 23%) and the title compound (24 mg, 59%) ($[\alpha]_D$ −46, *c* 1.0, $CHCl_3$). NMR data for (–)-**84ssa** (Pg = TES) closely matched those reported above for (±)-**84ssa** (Pg = TES).

colorless liquid, TLC R_f = 0.3 (50% Et_2O in hexanes).



(84sss (Pg = TES))

(1*R*,2*R*,4*S*,5*R*,6*R*)-*rel*-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-3-(triethylsilyl)oxy-1-((*S*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one (84sss (Pg = TES)).

From aldol (Li (*Z*)-enolate). See the preparation of **84ass** (Pg = TES). From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of **65b** (50 mg, 0.14 mmol) with **29a** (56 mg, 0.56 mmol) according to the general procedure (using $TiCl_2$(O*i*-Pr)$_2$; 16 h aldol reaction time) gave a crude product whose

^{1}H NMR spectrum indicated the presence of a 1:0.09:0.1:0.14:0.35 mixture of **84sss** (Pg = TES), **84ass** (Pg = TES), **84sas** (Pg = TES), **84aas** (Pg = TES) (tentatively identified), and **65b**, respectively. Fractionation of the crude product by FCC (30-50% Et_2O in hexanes) provided the title compound (44 mg, 58%).

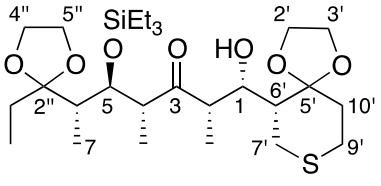
colorless oil, TLC R_f = 0.60 (70% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3510, 1696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (1H, ddd, *J* = 1.5, 3.5, 5.5 Hz, HC-1), 4.06 (1H, dd, *J* = 3, 6.5 Hz, HC-5), 4.01-3.91 (8H, m, H_2CO ×4), 3.40 (1H, d, *J* = 1.5 Hz, HO), 3.22 (1H, dq, *J* = 6.5, 7 Hz, HC-4), 3.05 (1H, dq, *J* = 3.5, 7 Hz, HC-2), 3.00-2.92 (2H, m, H_2C-7'), 2.71-2.65 (2H, m, H_2C-9'), 2.10-1.97 (3H, m, HC-6, HC-6', HC-10'), 1.73-1.67 (3H, m, HC-10', H_2CC-2''), 1.18 (3H, d, *J* = 7 Hz, H_3CC-2), 1.06 (3H, d, *J* = 7 Hz, H_3CC-4), 1.03 (3H, d, *J* = 7 Hz, H_3C-7), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.88 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.61 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.7 (s, C-3), 113.3 (s, C-2''), 109.5 (s, C-5'), 76.2 (d, C-5), 67.7 (d, C-1), 65.5 (t, CH_2O), 65.1 (t, CH_2O), 64.7 (t, CH_2O), 64.3 (t, CH_2O), 50.1 (d, C-2), 47.2 (d, C-4), 46.9 (d, C-6'), 45.0 (d, C-6), 35.3 (t, C-10'), 29.0 (t, CH_2C-2''), 28.4 (t, C-7'), 26.8 (t, C-9'), 15.6 (q, CH_3C-4), 10.7 (q, CH_3C-2), 10.6 (q, C-7), 8.1 (q, CH_3CC-2''), 7.2 (q ×3, CH_3CSi), 5.2 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{50}O_7SSi+Na^+$ 569.2938, found 569.2951 (ESI).

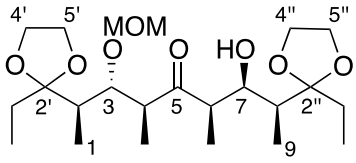


((–)-84sss (Pg = TES))

(1*S*,2*S*,4*R*,5*S*,6*S*)-(–)-6-(2-Ethyl-1,3-dioxolan-2-yl)-1-hydroxy-2,4-dimethyl-3-(triethylsilyl)oxy-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)heptan-3-one ((–)-84sss (Pg = TES)).

From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of (–)-**65b** (81% *ee*; 50 mg, 0.14 mmol) with **29a** (105 mg, 0.56 mmol) according to the general procedure (using $TiCl_2(Oi\text{-}Pr)_2$; 16 h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 1:0.15:0.25:0.36:0.23 mixture of **84sss** (Pg = TES), **84ass** (Pg = TES), **84sas** (Pg = TES), **84aas** (Pg = TES) (tentatively identified), and **65b**, respectively. Fractionation of the crude product by FCC (30-50% Et_2O in hexanes) provided the title compound (42 mg, 55%) ($[\alpha]_D$ −25, *c* 1.0, $CHCl_3$). NMR data for (−)-**84sss** (Pg = TES) closely matched those reported above for (±)-**84sss** (Pg = TES).

colorless oil, TLC R_f = 0.6 (70% Et_2O in hexanes).



(85sss (Pg = MOM))

(2*R*,3*R*,4*S*,6*R*,7*R*,8*S*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(methoxymethoxy)-4,6-dimethylnonan-5-one (85sss (Pg = MOM)).

From aldol (Li (*Z*)-enolate). See the preparation of **88ass** (Pg = MOM). From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of **65a** (41 mg, 0.14 mmol) with **29a** (53 mg, 0.34 mmol) according to the general procedure (using $TiCl(Oi\text{-}Pr)_3$; 5 h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 5:1 mixture of **88sss** (Pg = MOM) and **88ass** (Pg = MOM), respectively. Fractionation of the crude product by FCC (35% Et_2O in hexanes) afforded **88ass** (Pg = MOM) (7 mg, 11%) and the title compound (44 mg, 69%). From desulfurization. The crude product obtained by desulfurization of **84sss** (Pg = MOM) (13 mg, 0.027 mmol) according to the general procedure (24 h) was fractionated by PTLC (20% ethyl acetate in hexanes) to give the titled compound (7 mg, 58%).

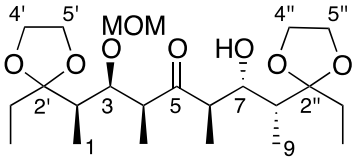
colorless viscous oil, TLC R_f = 0.3 (40% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3521, 1708 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (1H, d, *J* = 6.5 Hz, HCO_2), 4.50 (1H, d, *J* = 6.5 Hz, HCO_2), 4.12 (1H, br dd, *J* = 2.5, 8 Hz, HC-7), 4.00-3.91 (8H, m, H_2CO ×4), 3.77 (1H, dd, *J* = 2.5, 9 Hz, HC-3), 3.32 (1H, dq, *J* = 9, 7 Hz, HC-4), 3.30 (3H, s, *J* = Hz, H_3CO), 3.22 (1H, br s, HO), 2.92 (1H, dq, *J* = 8, 7.5 Hz, HC-6), 2.22 (1H, dq, *J* = 2.5, 7 Hz, HC-2), 2.04 (1H, dq, *J* = 2.5, 7 Hz, HC-8), 1.80-1.68 (2H, m, H_2CC-2'), 1.70 (2H, ap q, *J* = 7.5 Hz, H_2CC-2"), 1.21 (3H, d, *J* = 7 Hz, H_3CC-6), 1.08 (3H, d, *J* = 7 Hz, H_3C-1), 1.07 (3H, d, *J* = 7 Hz, H_3CC-4), 0.97 (3H, d, *J* = 7 Hz, H_3C-9), 0.89 (6H, ap t, *J* = 7.5 Hz, H_3CC-2', H_3CC-2").

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3 (s, C-5), 114.8 (s, C-2"), 113.4 (s, C-2'), 98.1 (t, OCH_2O), 83.5 (d, C-3), 70.7 (d, C-7), 65.6 (t, CH_2O), 65.5 (t, CH_2O), 65.1 (t, CH_2O), 65.0 (t, CH_2O), 56.3 (q, CH_3O), 51.1 (d, C-6), 47.4 (d, C-4), 41.6 (d, C-2), 39.9 (d, C-8), 29.0 (t, CH_2C-2'), 27.7 (t, CH_2C-2"), 15.3 (q, CH_3C-4), 13.2 (q, CH_3C-6), 11.6 (q, C-1), 8.4 (q, C-9), 8.0 (q, CH_3CC-2'), 7.9 (q, CH_3CC-2").

HRMS *m/z* calcd for $C_{23}H_{42}O_8$+Na^+ 469.2771, found 469.2767 (ESI).



(85sas (Pg = MOM))

(2*R*,3*S*,4*S*,6*R*,7*S*,8*R*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(methoxymethoxy)-4,6-dimethylnonan-5-one (85sas (Pg = MOM)).

From aldol (B (*E*)-enolate). Aldol reaction of **62a** (31 mg, 0.11 mmol) with **29b** (34 mg, 0.21 mmol) according to the general procedure (enolization conditions A: *c*-Hex_2BCl, equiv, – °C, h) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 3:1 mixture of a single aldol adduct (>19:1 dr) and **62a**, respectively. Fractionation of the crude by FCC (30-50% Et_2O in hexanes) gave recovered **62a** (5 mg, 16%) and the title compound (35 mg, 73%).

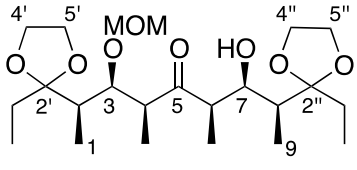
colorless oil, TLC R_f = 0.41 (50% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3525, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (1H, d, *J* = 6.5 Hz, HCO_2), 4.61 (1H, d, *J* = 6.5 Hz, HCO_2), 4.09 (1H, dd, *J* = 3, 6 Hz, HC-3), 4.09 (1H, br d, *J* = 9.5 Hz, HC-7), 4.00-3.92 (8H, m, H_2CO ×4), 3.36 (3H, s, H_3CO), 3.08 (1H, d, *J* = 1 Hz, HO), 2.98 (1H, dq, *J* = 6, 7 Hz, HC-4), 2.86 (1H, dq, *J* = 9.5, 7 Hz, HC-6), 2.01 (1H, dq, *J* = 3, 7 Hz, HC-2), 1.94 (1H, br q, *J* = 7 Hz, HC-8), 1.77-1.66 (4H, m, H_2CC-2', H_2CC-2''), 1.15 (3H, d, *J* = 7 Hz, H_3CC-4), 0.96 (3H, d, *J* = 7 Hz, H_3C-1), 0.93 (3H, d, *J* = 7 Hz, H_3C-9), 0.90 (3H, d, *J* = 7 Hz, H_3CC-6), 0.864 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.860 (3H, t, *J* = 7.5 Hz, H_3CCC-2').

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.7 (s, C-5), 114.7 (s, C-2''), 113.8 (s, C-2'), 98.2 (t, OCH_2O), 76.8 (d, C-3), 72.8 (d, C-7), 65.8 (t, CH_2O), 65.23 (t, CH_2O), 65.19 (t, CH_2O), 64.9 (t, CH_2O), 56.5 (q, CH_3O), 52.3 (d, C-4), 48.6 (d, C-6), 42.7 (d, C-2), 38.5 (d, C-8), 28.2 (t, CH_2C-2''), 27.2 (t, CH_2C-2'), 14.1 (q, CH_3C-6), 12.3 (q, CH_3C-4), 10.3 (q, C-1), 8.3 (q, CH_3CC-2''), 7.6 (q, CH_3CC-2'), 6.6 (q, C-9).

HRMS *m/z* calcd for $C_{23}H_{42}O_8$+Na^+ 469.2771, found 469.2786 (ESI).



(85sss (Pg = MOM))

(2*R*,3*S*,4*S*,6*R*,7*R*,8*S*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-3-(methoxymethoxy)-4,6-dimethylnonan-5-one (85sss (Pg = MOM)).

From aldol (B (*Z*)-enolate). Aldol reaction of **62a** (30 mg, 0.10 mmol) with **29b** (33 mg, 0.20 mmol) according to the general procedure (enolization conditions: –78 °C, 2 h) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 54:24:14:8:25 mixture of **85sss** (Pg = MOM), **85ssa** (Pg = MOM), **85ass** (Pg = MOM), **85sas** (Pg = MOM), and **62a**, respectively, along with other unidentified minor components (<5%). Fractionation of the crude product by FCC (30-60% ether in hexanes) gave recovered **62a** (6 mg, 20%), a 56:26:12:6 mixture of **85sss** (Pg = MOM), **85ssa** (Pg = MOM), **85ass** (Pg = MOM), and **85sas** (Pg = MOM), respectively (19 mg, 41%), and a 10:3:1 mixture of **85sss** (Pg = MOM), **85ssa** (Pg = MOM), and **85ass** (Pg = MOM), respectively (16 mg, 34%). The NMR signals for the major component of the above mixtures

closely matched those for the pure **85sss** (Pg = MOM) obtained as described below. The ^{1}H NMR signals for the minor **85sas** (Pg = MOM) component of the above mixture matched those for the pure **85sas** (Pg = MOM) obtained as described above. Adducts **85ssa** (Pg = MOM) and **85ass** (Pg = MOM) were identified by conversion of the latter mixture to the corresponding 3,7-bis-*O*-MOM derivatives **91** (see below). From desulfurization. The crude product obtained from desulfurization of **81sss** (Pg = MOM) (11 mg, 0.023 mmol) according to the general procedure (16 h) was fractionated by PTLC (50% ethyl acetate in hexanes) to give the title compound (10 mg, 97%).

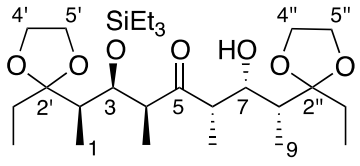
colorless oil, TLC R_f = 0.29 (60% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3519, 1703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67 (1H, d, *J* = 6.5 Hz, HCO_2), 4.57 (1H, d, *J* = 6.5 Hz, HCO_2), 4.10 (1H, ddd, *J* = 1, 2.5, 7.5 Hz, HC-7), 4.00-3.89 (9H, m, HC-3, H_2CO ×4), 3.36 (3H, s, H_3CO), 3.23 (1H, d, *J* = 1 Hz, HO), 3.02 (1H, dq, *J* = 5, 7 Hz, HC-4), 3.00 (1H, dq, *J* = 7.5, 7 Hz, HC-6), 1.99 (1H, dq, *J* = 3, 7 Hz, HC-2), 1.96 (1H, dq, *J* = 2.5, 7 Hz, HC-8), 1.73-1.60 (4H, m, H_2CC-2', H_2CC- 2"), 1.21 (3H, d, *J* = 7 Hz, H_3CC-6), 1.11 (3H, d, *J* = 7 Hz, H_3CC-4), 0.95 (3H, d, *J* = 7 Hz, H_3C-9), 0.92 (3H, d, *J* = 7 Hz, H_3C-1), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2"), 0.86 (3H, t, *J* = 7.5 Hz, H_3CCC-2').

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1 (s, C-5), 114.7 (s, C-2"), 113.5 (s, C-2'), 97.5 (t, OCH_2O), 77.1 (d, C-3), 71.0 (d, C-7), 65.5 (t, CH_2O), 65.2 (t, CH_2O), 65.1 (t, CH_2O), 65.0 (t, CH_2O), 56.4 (q, CH_3O), 50.2 (d, C-4), 49.8 (d, C-6), 41.6 (d, C-2), 40.0 (d, C-8), 27.7 (t, CH_2C-2"), 26.9 (t, CH_2C-2'), 14.0 (q, CH_3C-6), 12.8 (q, CH_3C-4), 10.7 (q, C-1), 8.3 (q, C-9), 7.9 (q, CH_3CC-2"), 7.7 (q, CH_3CC-2').

HRMS *m/z* calcd for $C_{23}H_{42}O_8$+Na^+ 469.2771, found 469.2759 (ESI).



(85ass (Pg = TES))

(2*R*,3*S*,4*S*,6*S*,7*S*,8*R*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-4,6-dimethyl-3-((triethylsilyl)oxy)nonan-5-one (85ass (Pg = TES)).

From aldol (Li (*Z*)-enolate). Aldol reaction of **62b** (30 mg, 0.084 mmol) with **29b** (27 mg, 0.17 mmol) according to the general procedure gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 44:27:17:7:4:1:20 mixture of **85ass** (Pg = TES), **85sss** (Pg = TES), **85asa** (Pg = TES), **85ssa** (Pg = TES), **85aas** (Pg = TES) (tentatively identified), **85sas** (Pg = TES), and **62b**, respectively. Fractionation of the crude product by FCC (30-40% Et_2O in hexanes) gave recovered **62b** (3 mg, 10%), a 3:1 mixture of **85aas** (Pg = TES) and **8sas** (Pg = TES) (5 mg; ca. 8% pure), a 12:4:3 mixture of **85sss** (Pg = TES), **85ass** (Pg = TES) and **85ssa** (Pg = TES) (9 mg, 21%), and a 58:23:15:4 mixture of **85ass** (Pg = TES), **85asa** (Pg = TES), **85sss** (Pg = TES), and **85ssa** (Pg = TES) (25 mg). The latter fraction was further fractionated by PTLC (10% Et_2O in CH_2Cl_2) to afford a 5:2:1 mixture of **85ass** (Pg = TES), **85sss** (Pg = TES) and **85ssa** (Pg = TES) (8 mg, 18%), a 20:5:2 mixture of **85ass** (Pg = TES), **85sss** (Pg = TES), and **85asa** (Pg = TES) (9 mg, 21%), and the title compound (7 mg, 16%).

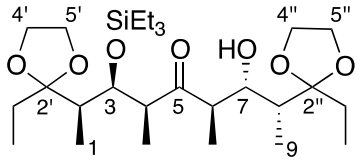
colorless liquid, TLC R_f = 0.36 (40% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3532, 1703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (1H, dd, *J* = 3.5, 5.5 Hz, HC-3), 4.06 (1H, br d, *J* = 8.5 Hz, HC-7), 4.01-3.87 (8H, m, H_2CO ×4), 3.07 (1H, br s, HO), 2.96 (1H, dq, *J* = 5.5, 7 Hz, HC-4), 2.93 (1H, dq, *J* = 8.5, 7 Hz, HC-6), 1.86 (1H, dq, *J* = 3.5, 7 Hz, HC-2), 1.84 (1H, br q, *J* = 7 Hz, HC-8), 1.69 (2H, ap q, H_2CC-2''), 1.68 (1H, dq, *J* = 14.5, 7.5 Hz, HCC-2'), 1.19 (3H, d, *J* = 7 Hz, H_3CC-6), 1.04 (3H, d, *J* = 7 Hz, H_3CC-4), 0.958 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 1.61 (1H, dq, *J* = 14.5, 7.5 Hz, HCC-2'), 0.955 (3H, d, *J* = 7 Hz, H_3C-9), 0.89 (3H, d, *J* = 7 Hz, H_3C-1), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.84 (3H, t, *J* = 7.5 Hz, H_3CCC-2'), 0.64 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.8 (s, C-5), 114.8 (s, C-2''), 113.8 (s, C-2'), 71.6 (d, C-7), 71.4 (d, C-3), 65.7 (t, CH_2O), 65.2 (t, CH_2O), 65.1 (t, CH_2O), 65.0 (t, CH_2O), 52.5 (d, C-4), 49.4 (d, C-6), 42.8 (d, C-2), 39.9 (d, C-8), 28.1 (t, CH_2C-2''), 27.4 (t, CH_2C-2'), 14.2 (q, CH_3C-6), 12.8 (q, CH_3C-4), 10.6 (q, C-1), 8.1 (q, CH_3CC-2''), 7.7 (q, CH_3CC-2'), 7.6 (q, C-9), 7.3 (q ×3, CH_3CSi), 5.6 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{52}O_7Si+Na^+$ 539.3375, found 539.3374 (ESI).



(85sas (Pg = TES))

(2*R*,3*S*,4*S*,6*R*,7*S*,8*R*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-4,6-dimethyl-3-((triethylsilyl)oxy)nonan-5-one (85sas (Pg = TES)).

From aldol (B (*E*)-enolate). Aldol reaction of **62b** (32 mg, 0.089 mmol) with **29b** (42 mg, 0.27 mmol) according to the general procedure (enolization conditions A: *c*-Hex_2BCl, 2 equiv, 0 °C, 30 min) gave a crude product whose ^1H NMR spectrum indicated the presence of a single aldol adduct (dr >19:1). Fractionation of the crude by FCC (20-30% Et_2O in hexanes) gave the title compound (43 mg, 93%). An analogous reaction of **62b** (32 mg, 0.09 mmol) with **29b** (42 mg, 0.23 mmol) (enolization conditions B; *c*-Hex_2BCl, 1.6 equiv) afforded recovered **62b** (2 mg, 6%) and titled compound (41 mg, 89%). From desulfurization. The crude product obtained from desulfurization of **81sas** (Pg = TES) (10 mg, 0.018 mmol) according to the general procedure (1.5 h) was fractionated by FCC (20% ethyl acetate in hexanes) to afford the title compound (9 mg, 95%).

colorless oil, TLC R_f = 0.35 (20% ethyl acetate in hexanes).

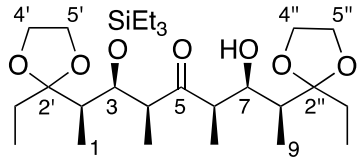
IR (DRIFT) ν_{max} 3532, 1709 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (1H, dd, *J* = 4, 5 Hz, HC-3), 4.05 (1H, br d, *J* = 9.5 Hz, HC-7), 4.00-3.87 (8H, m, H_2CO ×4), 2.96 (1H, dq, *J* = 5, 7 Hz, HC-4), 2.94 (1H, s, HO), 2.85 (1H, dq, *J* = 9.5, 7 Hz, HC-6), 2.00-1.96 (2H, m, HC-2, HC-8), 1.75-1.61 (4H, m, H_2CC-2', H_2CC-2"), 1.11 (3H, d, *J* = 7 Hz, H_3CC-4), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.94 (3H, d, *J* = 7 Hz, H_3C-9), 0.91 (3H, d, *J* = 7 Hz, H_3CC-6), 0.90 (3H, d, *J* = 7 Hz, H_3C-1), 0.87 (3H, t, *J* = 7.5 Hz, H_3CCC-2"), 0.84 (3H, t, *J* = 7.5 Hz, H_3CCC-2'), 0.54 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3 (s, C-5), 114.8 (s, C-2"), 113.9 (s, C-2'), 73.3 (d, C-7), 71.2 (d, C-3), 65.8 (t, CH_2O), 65.2 (t ×2, CH_2O), 64.9 (t, CH_2O), 53.6 (d, C-4), 47.9 (d, C-6), 42.9 (d,

C-2), 38.5 (d, C-8), 28.3 (t, CH_2C-2''), 27.5 (t, CH_2C-2'), 13.8 (q, CH_3C-6), 12.6 (q, CH_3C-4), 10.6 (q, C-1), 8.4 (q, CH_3CC-2''), 7.5 (q, CH_3CC-2'), 7.4 (q ×3, CH_3CSi), 6.6 (q, C-9), 5.6 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{52}O_7Si+Na^+$ 539.3375, found 539.3366 (ESI).



(85sss (Pg = TES))

(2*R*,3*S*,4*S*,6*R*,7*R*,8*S*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-7-hydroxy-4,6-dimethyl-3-((triethylsilyl)oxy)nonan-5-one (85sss (Pg = TES)).

From aldol (B (*Z*)-enolate). Aldol reaction of **62b** (53 mg, 0.15 mmol) with **29b** (48 mg, 0.30 mmol) according to the general procedure (enolization conditions: –78 °C, 4 h) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 15:5:2:1:7 mixture of **85sss** (Pg = TES), **85ssa** (Pg = TES), **85sas** (Pg = TES), **85ass** (Pg = TES), and **62b**, respectively. Fractionation of the crude by FCC (10-20% acetone in hexanes) gave recovered **62b** (9 mg, 17%) and the title compound as an inseparable 2.6:1 mixture with **85ssa** (Pg = TES), respectively (44 mg, 58%). The NMR signals for the major component of the mixture matched those for obtained for pure **85sss** (Pg = TES) obtained as described below. Adduct **85ssa** (Pg = TES) was identified by conversion of the mixture to the corresponding 3,7-bis-*O*-TES derivatives **94** (see below). From aldol (Ti(IV) (*Z*)-enolate). Aldol reaction of **62b** (46 mg, 0.13 mmol) with **29b** (59 mg, 0.37 mmol) according to the general procedure (using TiCl(O*i*-Pr)$_3$; 6 h aldol reaction time) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 10:2:1:3 mixture of **85sss** (Pg = TES), **85ssa** (Pg = TES), **85ass** (Pg = TES), and **62b**, respectively. Fractionation of the crude by FCC (20% Et_2O in hexanes) gave recovered **62b** (8 mg, 17%) and the title compound as an inseparable 5:1 mixture of **85sss** (Pg = TES) and **85ssa** (Pg = TES) (40 mg, 81%). The NMR signals for the major component of the mixture matched those for obtained for pure **85sss** (Pg = TES) obtained as described below. Adduct **85ssa** (Pg = TES) was identified by conversion of the above 2.6:1 mixture to the corresponding 3,7-bis-*O*-TES derivatives **94**. From desulfurization. The crude product obtained from desulfurization of **81sss** (Pg = TES) (10 mg, 0.02 mmol) according to the general

procedure (1 h) was fractionated by PTLC (40% ethyl acetate in hexanes) to give the title compound (9 mg, 95%).

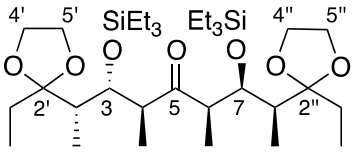
colorless oil, TLC R_f = 0.31 (40% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3521, 1702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (1H, dd, *J* = 4, 4 Hz, HC-3), 4.07 (1H, dd, *J* = 2, 8 Hz, HC-7), 3.99-3.86 (8H, m, H_2CO ×4), 3.21 (1H, br s, HO), 2.97-2.92 (2H, m, HC-4, HC-6), 1.92-1.84 (2H, m, HC-2, HC-8), 1.71-1.60 (3H, m, HCC-2', H_2CC-2''), 1.56 (1H, dq, *J* = 14.5, 7.5 Hz, HCC-2'), 1.20 (3H, d, *J* = 7 Hz, H_3CC-6), 1.09 (3H, d, *J* = 7 Hz, H_3CC-4), 0.954 (9H, t, *J* = 8 Hz, H_3CCSi), 0.948 (3H, d, *J* = 7 Hz, H_3C-9), 0.87 (3H, d, *J* = 7 Hz, H_3C-1), 0.85 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.83 (3H, t, *J* = 7.5 Hz, H_3CCC-2''), 0.64 (6H, ap q, *J* = 8 Hz, H_2CSi).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3 (s, C-5), 114.6 (s, C-2''), 113.7 (s, C-2'), 71.9 (d, C-3), 71.3 (d, C-7), 65.6 (t, CH_2O), 65.2 (t, CH_2O), 65.1 (t, CH_2O), 65.0 (t, CH_2O), 52.1 (d, C-4), 49.7 (d, C-6), 42.1 (d, C-2), 40.1 (d, C-8), 27.8 (t, CH_2C-2''), 27.0 (t, CH_2C-2'), 13.9 (q, CH_3C-6), 12.9 (q, CH_3C-4), 10.9 (q, H_3C-1), 8.1 (q, H_3C-9), 7.9 (q, H_3CCC-2''), 7.5 (q, H_3CCC-2'), 7.3 (q ×3, CH_3CSi), 5.5 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{27}H_{52}O_7Si+Na^+$ 539.3375, found 539.3365 (ESI).



(90)

(2*S*,3*R*,4*S*,6*R*,7*R*,8*S*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-4,6-dimethyl-3,7-bis((triethylsilyl)oxy)nonan-5-one (90).

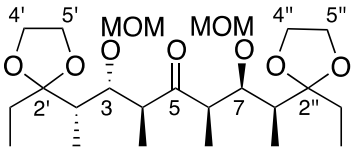
Reaction of **85sas** (Pg = TES) (51 mg, 0.10 mmol) with Et_3Si-Cl and imidazole for 2 days according to the general procedure gave the title compound (60 mg, 97%) after fractionation of the crude product by FCC (5% ethyl acetate in hexanes). The identical product (95% yield) was obtained by others from an analogous reaction of **86sss** (Pg = TES).

colorless oil, TLC R_f = 0.4 (10% ethyl acetate in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (1H, dd, *J* = 3.5, 5.5 Hz), 4.20 (1H, dd, *J* = 1, 3.5 Hz), 3.95-3.78 (8H, m), 3.04 (1H, dq, *J* = 3.5, 7 Hz), 2.90 (1H, dq, *J* = 3.5, 7 Hz), 2.95 (1H, dq, *J* = 1, 7 Hz), 1.81 (1H, dq, *J* = 5.5, 7 Hz), 1.73-1.54 (4H, m), 1.20 (3H, d, *J* = 7 Hz), 1.04 (3H, d, *J* = 7 Hz), 0.98 (9H, t, *J* = 8 Hz), 0.95 (3H, d, *J* = 7 Hz), 0.94 (9H, t, *J* = 8 Hz), 0.92 (3H, d, *J* = 7 Hz), 0.84 (3H, t, *J* = 7.5 Hz), 0.81 (3H, t, *J* = 7.5 Hz), 0.69-0.58 (12H , m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 113.9, 113.6, 71.3, 69.5, 65.3, 65.2, 65.1, 64.8, 51.72, 51.68, 43.7, 40.1, 26.7, 26.0, 11.9, 11.7, 11.0, 10.8, 7.4 (×3), 7.3, 7.2 (×3), 7.1, 5.7 (×3), 5.6 (×3).

HRMS *m/z* calcd for $C_{33}H_{66}O_7Si_2$+Na^+ 653.4239, found 653.4219 (ESI).



(91)

(2*S*,3*R*,4*S*,6*R*,7*R*,8*S*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-4,6-dimethyl-3,7-bis(methoxymethoxy)nonan-5-one (91).

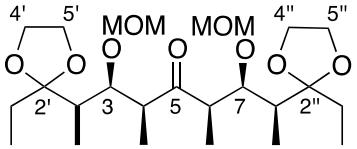
Reaction of **85sas** (Pg = MOM) (26 mg, 0.058 mmol) with MOM-Cl and *i*-Pr_2EtN for 3 days according to the general procedure gave the title compound (27 mg, 98%) after fractionation of the crude product by PTLC (40% ethyl acetate in hexanes). The identical product (95% yield) was obtained by others from an analogous reaction of **86sss** (Pg = MOM).

colorless oil, TLC R_f = 0.6 (40% Et_2O in benzene).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67-4.66 (2H, ap d, *J* = 6 Hz), 4.62 (1H, d, *J* = 6 Hz), 4.57 (1H, d, *J* = 6 Hz), 4.13 (1H, dd, *J* = 4, 5 Hz), 3.98-3.89 (9H, m), 3.37 (3H, s), 3.34 (3H, s), 3.16 (1H, dq, *J* = 6.5, 7 Hz), 2.88 (1H, dq, *J* = 5, 7 Hz), 2.03 (1H, dq, *J* = 1.5, 7 Hz), 1.94 (1H, dq, *J* = 4, 7 Hz), 1.77-1.61 (4H, m), 1.23 (3H, d, *J* = 7 Hz), 1.06 (3H, d, *J* = 7 Hz), 0.99 (3H, d, *J* = 7 Hz), 0.98 (3H, d, *J* = 7 Hz), 0.86 (3H, t, *J* = 7.5 Hz), 0.85 (3H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ215.0, 113.63, 113.61, 98.3, 97.1, 76.9, 76.5, 65.4 (×2), 65.2, 65.1, 56.6, 56.3, 51.8, 48.9, 48.9, 42.8, 40.4, 27.1, 26.9, 13.4, 12.2, 10.7, 10.4, 7.8, 7.5.

HRMS *m/z* calcd for $C_{25}H_{46}O_9$+Na^+ 513.3034, found 513.3035 (ESI).



(92a)

(2*R*,3*S*,4*S*,6*R*,7*R*,8*S*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-4,6-dimethyl-3,7-bis((triethylsilyl)oxy)nonan-5-one (92a).

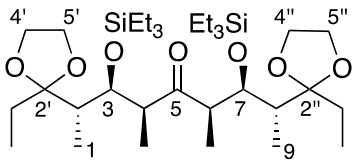
Reaction of **85sss** (Pg = MOM) (20 mg, 0.045 mmol) with MOM-Cl and *i*-Pr_2EtN for 48 h according to the general procedure gave the title compound (22 mg, quantitative) after fractionation of the crude product by PTLC (50% ethyl acetate in hexanes).

colorless liquid, TLC R_f = 0.62 (50% ethyl acetate in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (2H, d, *J* = 6 Hz, HCO_2 ×2), 4.62 (2H, d, *J* = 6 Hz, HCO_2 ×2), 4.01 (2H, dd, *J* = 3, 5.5 Hz, HC-3, HC-7), 3.97-3.91 (8H, m, H_2CO ×4), 3.37 (6H, s, H_3CO ×2), 3.03 (2H, dq, *J* = 5.5, 7 Hz, HC-4, HC-6), 1.94 (2H, dq, *J* = 3, 7 Hz, HC-2, HC-8), 1.75-1.65 (4H, m, H_2CC-2', H_2CC-2"), 1.15 (6H, d, *J* = 7 Hz, H_3CC-4, H_3CC-6), 0.95 (6H, d, *J* = 7 Hz, H_3C-1, H_3C-9), 0.86 (6H, t, *J* = 7.5 Hz, H_3CCC-2', H_3CCC-2").

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8, 113.6 (×2), 97.9 (×2), 77.0 (×2), 65.3 (×2), 65.2 (×2), 56.5 (×2), 50.4 (×2), 42.3 (×2), 27.0 (×2), 13.2 (×2), 10.4 (×2), 7.6 (×2).

HRMS *m/z* calcd for $C_{25}H_{46}O_9$+Na^+ 513.3034, found 513.3021 (ESI).



(92b)

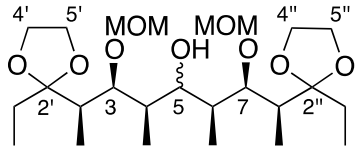
(2*S*,3*S*,4*S*,6*R*,7*R*,8*R*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-3,7-bis(triethylsilyloxy)-4,6-dimethylnonan-5-one (92b).

Reaction of **83ssa** (Pg = TES) (18 mg, 0.033 mmol) with Et_3SiCl and imidazole for 16 h according to the general procedure gave the crude product (24 mg). Desulfurization for 1 h according to the general procedure to afford the crude product which was fractionated by FCC (10% ethyl acetate in hexanes) to give the title compound (15 mg, 72% based on starting aldol).

colorless liquid, TLC R_f = 0.55 (10% ethyl acetate in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.42 (2H, dd, *J* = 3, 4.5 Hz), 3.94-3.83 (8H, m), 3.13 (2H, dq, *J* = 4.5, 7 Hz), 2.01 (2H, dq, *J* = 3, 7 Hz), 1.72-1.57 (4H, m), 1.13 (6H, d, *J* = 7 Hz), 0.99 (6H, d, *J* = 7 Hz), 0.94 (18H, t, *J* = 8 Hz), 0.87 (6H, t, *J* = 7.5 Hz), 0.60 (12H, ap q, *J* = 8 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ 216.4, 113.4, 71.3, 65.7, 65.0, 46.8, 45.6, 28.8, 13.2, 10.7, 8.1, 7.2, 5.4.



(93a)

(2*R*,3*S*,4*S*,6*R*,7*R*,8*S*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-4,6-dimethyl-3,7-bis(methoxymethoxy)nonan-5-ol (93a).

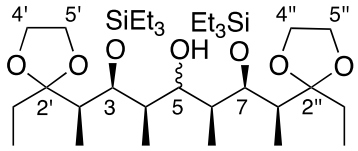
$LiEt_3BH$ (1.0 M in THF, 0.030 mL, 0.03 mmol) was added to a stirred solution of the **92a** (11 mg, 0.022 mmol) in THF (0.4 mL) at 0 °C under argon. The reaction vessel was removed from the ice bath and stirring was continued at ambient temperature. After 1 day, the reaction mixture was cooled to 0 °C and quenched by addition of saturated aq NH_4Cl. The mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a 3.8:1 mixture of diastereomers. Fractionation of the crude by PTLC (80% Et_2O in hexanes) gave the title compound as a 3.8:1 mixture of C_S symmetric diastereomers (9 mg, 82%).

colorless liquid, TLC R_f = 0.46 (50% ethyl acetate in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (2H, d, *J* = 6 Hz), 4.58 (2H, d, *J* = 6 Hz), 3.99-3.93 (9H, m), 3.75 (1H, t, *J* = 5 Hz), 3.73 (2H, dd, *J* = 3.5, 3.5 Hz), 3.39 (6H, s), 2.14 (2H, dq, *J* = 3.5, 7.5 Hz), 1.79 (2H, ddq, *J* = 3.5, 5, 7 Hz), 1.72-1.60 (4H, m), 1.00 (6H, d, *J* = 7 Hz), 0.96 (6H, d, *J* = 7.5 Hz), 0.867 (6H, t, *J* = 7.5 Hz), δ for minor isomer (partial data) 4.73 (2H, d, *J* = 6 Hz), 4.65 (2H, d, *J* = 6 Hz), 4.11 (2H, dd, *J* = 2, 4.5 Hz), 3.40 (6H, s), 2.01 (2H, dq, *J* = 4.5, 7.5 Hz), 1.84 (2H, ddq, *J* = 2, 7, 7 Hz), 0.98 (6H, d, *J* = 7 Hz), 0.872 (6H, t, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 114.04 (×2), 97.5 (×2), 78.1 (×2), 75.3, 65.4 (×2), 64.9 (×2), 56.4 (×2), 42.5 (×2), 42.4 (×2), 27.23 (×2), 11.5 (×2), 8.7 (×2), 8.2 (×2), δ for minor isomer 114.02 (×2), 98.0 (×2), 77.6, 75.9 (×2), 65.5 (×2), 65.0 (×2), 56.6 (×2), 43.5 (×2), 41.9 (×2), 27.25 (×2), 11.8 (×2), 11.4 (×2), 8.0 (×2).

HRMS *m/z* calcd for $C_{25}H_{48}O_9$+Na^+ 515.3190, found 515.3203 (ESI).



(93b)

(2*R*,3*S*,4*S*,6*R*,7*R*,8*S*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-4,6-dimethyl-3,7-bis((triethylsilyl)oxy)nonan-5-ol (93b).

$LiEt_3BH$ (1.0 M in THF, 0.020 mL, 0.02 mmol) was added to a stirred solution of the **92b** (11 mg 0.017 mmol) in THF (0.4 mL) at 0 °C under argon. The reaction vessel was removed from the ice bath and stirring was continued at ambient temperature. After 3 days, the reaction mixture was cooled to 0 °C and quenched by addition of saturated aq NH_4Cl. The mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a single diastereomer. Fractionation of the crude by PTLC (15% ethyl acetate in hexanes) gave the title compound as a single diastereomer of unknown configuration at C-5 (10 mg, 91%).

colorless liquid, TLC R_f = 0.67 (20% ethyl acetate in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (2H, dd, *J* = 3, 3.5 Hz), 3.96-3.90 (8H, m), 3.48 (1H, d, *J* = 4 Hz), 3.36 (1H, dt, *J* = 4, 6.5 Hz), 1.95 (2H, dq, *J* = 3.5, 7 Hz), 1.79 (2H, ddq, *J* = 3, 6.5, 7 Hz), 1.69 (2H, dq, *J* = 14.5, 7.5 Hz), 1.62 (2H, dq, *J* = 14.5, 7.5 Hz), 0.98 (6H, d, *J* = 7 Hz), 0.97 (18H, t, *J* = 8 Hz), 0.89 (6H, d, *J* = 7 Hz), 0.86 (6H, t, *J* = 7.5 Hz), 0.67 (12H, ap q, *J* = 8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 114.3 (×2), 76.8, 71.9 (×2), 65.0 (×2), 64.9 (×2), 43.6 (×2), 42.7 (×2), 26.9 (×2), 12.4 (×2), 11.6 (×2), 7.6 (×2), 7.4 (×6), 5.6 (×6).

HRMS *m/z* calcd for $C_{33}H_{68}O_7Si_2+Na^+$ 655.4395, found 655.4409 (ESI).

(94)

(2*R*,3*S*,4*S*,6*R*,7*R*,8*R*)-*rel*-2,8-Bis(2-ethyl-1,3-dioxolan-2-yl)-4,6-dimethyl-3,7-bis((triethylsilyl)oxy)nonan-5-one (94).

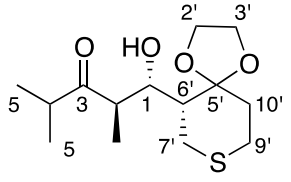
Reaction of a 3:1 mixture of **85sss** (Pg = TES)**l** and **85ssa** (Pg = TES), respectively (9 mg, 0.02 mmol), with Et_3Si-Cl and imidazole for 36 h according to the general procedure gave, after fractionation of the crude product by FCC (5% ethyl acetate in hexanes), an inseparable 3:1 mixture **92b** and the title compound, respectively (9 mg, 92%). The NMR data for the minor component matched those for the pure compound obtained by others from an analogous reaction of **87sss** (Pg = TES).

colorless oil, TLC R_f = 0.6 (60% Et_2O in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (1H, dd, *J* = 2.5, 3 Hz), 4.19 (1H, dd, *J* = 3, 5.5 Hz), 3.95-3.85 (8H, m), 3.10 (1H, dq, *J* = 2.5, 7 Hz), 2.96 (1H, dq, *J* = 5.5, 7 Hz), 2.01 (1H, dq, *J* = 3, 7 Hz), 1.75 (1H, dq, *J* = 3, 7 Hz), 1.72-1.55 (4H, m), 1.15 (3H, d, *J* = 7 Hz), 1.10 (3H, d, *J* = 7 Hz), 0.98 (3H, d, *J* = 7 Hz), 0.96 (9H, t, *J* = 8 Hz), 0.93 (9H, t, *J* = 8 Hz), 0.89 (3H, d, *J* = 7 Hz), 0.88 (3H, t, *J* = 7.5 Hz), 0.82 (3H, t, *J* = 7.5 Hz), 0.68-0.54 (12H, m).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8 (s), 113.7 (s), 113.1 (s), 72.9 (d), 69.1 (d), 65.7 (t), 65.4 (t), 65.2 (t), 64.9 (t), 49.8 (d), 48.3 (d), 46.1 (d), 43.2 (d), 28.9 (t), 27.4 (t), 13.8 (q), 12.8 (q), 10.3 (q), 9.9 (q), 8.2 (q), 7.42 (q), 7.41 (q ×3), 7.2 (q ×3), 5.7 (t ×3), 5.3 (t ×3).

HRMS *m/z* calcd for $C_{33}H_{66}O_7Si_2+Na^+$ 653.4239, found 653.4252 (ESI).



(113as)

(1*S*,2*R*)-*rel*-1-Hydroxy-2,4-dimethyl-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-pentan-3-one (113as).

Adapting the procedure reported by Evans *et al.*,[85] (*c*-Hex)$_2$BCl (1.0 M in hexanes; 0.64 mL, 0.64 mmol) and Et_3N (96 μL, 70 mg, 0.69 mmol) were sequentially added to a stirring solution of 2-methyl-3-pentanone (72 μL, 58 mg, 0.58 mmol) in Et_2O (2.5 mL) at 0 °C under Ar. After 1 h, the mixture was cooled to −78 °C, and a solution of **29a** (100 mg, 0.53 mmol) in Et_2O (0.5 mL) was added via syringe. After 16 h, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 7 mL), MeOH (7 mL), and 30% aq H_2O_2 (3.5 mL) with vigorous stirring. The reaction vessel was transferred to an ice bath, and after vigorous stirring for 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of a single aldol adduct (dr >19:1). Fractionation of the crude product by FCC (50% Et_2O in hexanes) provided the title compound (130 mg, 85%).

white solid, TLC R_f = 0.44 (60% Et_2O in hexanes).

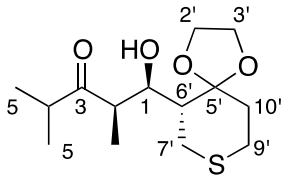
IR (DRIFT) ν_{max} 3492, 1707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 (1H, ddd, *J* = 1.5, 2, 9.5 Hz, HC-1), 4.10-3.91 (4H, m, H_2C-2' & H_2C-3'), 3.07 (1H, d, *J* = 2 Hz, HO), 3.05 (1H, dd, *J* = 11.5, 14 Hz, HC-7'), 2.92 (1H, dq, *J* = 9.5, 7 Hz, HC-2), 2.82 (1H, ddd, *J* = 2.5, 12.5, 13.5 Hz, HC-9'), 2.72 (1H, qq, *J* = 7, 7 Hz, HC-4), 2.62 (1H, ddd, *J* = 2, 3.5, 14 Hz, HC-7'), 2.52 (1H, ddd, *J* = 2, 3.5, 4, 13.5 Hz, HC-9'), 2.14 (1H,

ddd, *J* = 2.5, 4, 14 Hz, HC-10'), 2.02 (1H, ddd, *J* = 1.5, 3.5, 11.5 Hz, HC-6'), 1.73 (1H, ddd, *J* = 3.5, 12.5, 14 Hz, HC-10'), 1.10 (3H, d, *J* = 7 Hz, H_3C-5), 1.08 (3H, d, *J* = 7 Hz, H_3C-5), 0.98 (3H, d, *J* = 7 Hz, H_3CC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.5 (s, C-3), 110.4 (s, C-5'), 72.0 (d, C-1), 64.9 (t, C-2'), 64.4 (t, C-3'), 46.4 (d, C-6'), 46.3 (d, C-2), 42.0 (d, C-4), 36.5 (t, C-10'), 26.7 (t, C-9'), 25.9 (t, C-7'), 18.3 (q, C-5), 17.8 (q, C-5), 14.2 (q, CH_2C-2).

HRMS *m/z* calcd for $C_{14}H_{24}O_4S+Na^+$ 311.1287, found 311.1291 (ESI).



(113sa)

(1*R*,2*R*)-*rel*-1-Hydroxy-2,4-dimethyl-1-((*R*)-*rel*-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-pentan-3-one (113sa).

Isomerization of **113as** (50 mg, 0.17 mmol) according to the general procedure (*i*-PrMgBr, 6 d) gave a crude product that was a single aldol adduct by ^{1}H NMR. Fractionation of the crude product by FCC (40-50% Et_2O in hexanes) provided the title compound (42 mg, 84%).

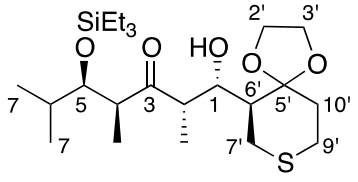
white solid, TLC R_f = 0.42 (50% Et_2O in hexanes).

IR (DRIFT) ν_{max} 3495, 1712 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (1H, br d, *J* = 8.5 Hz, HC-1), 4.05-3.96 (4H, m, H_2C-2' & H_2C-3'), 3.92 (1H, d, *J* = 1.5 Hz, HO), 2.97 (1H, qq, *J* = 7, 7 Hz, HC-4), 2.92 (1H, br d, *J* = 13.5 Hz, HC-7'), 2.85-2.78 (2H, m, HC-2 & HC-9'), 2.73-2.66 (1H, m, HC-9'), 2.62 (1H, dd, *J* = 6.5, 14 Hz, HC-7'), 2.21 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10'), 1.96 (1H, ddd, *J* = 3, 6.5, 8.5 Hz, HC-6'), 1.84 (1H, ddd, *J* = 3.5, 7, 13.5 Hz, HC-10'), 1.11 (3H, d, *J* = 6.5 Hz, H_3C-5), 1.10 (3H, d, *J* = 6.5 Hz, H_3C-5), 1.08 (3H, d, *J* = 7 Hz, H_3CC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2 (s, C-3), 110.7 (s, C-5'), 70.5 (d, C-1), 65.0 (t, C-2'), 64.2 (t, C-3'), 46.3 (d, C-2), 46.0 (d, C-6'), 37.9 (d, C-4), 34.3 (t, C-10'), 29.6 (t, C-7'), 27.0 (t, C-9'), 19.7 (q, C-5), 18.5 (q, C-5), 8.1 (q, CH_2C-2).

HRMS *m/z* calcd for $C_{14}H_{24}O_4S+Na^+$ 311.1287, found 311.1296 (ESI).



(117asa)

(1*S*,2*S*,4*S*,5*R*)-*rel*-1-Hydroxy-2,4,6-trimethyl-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)heptan-3-one (117asa).

For preparation, see the preparation of **117ssa.**

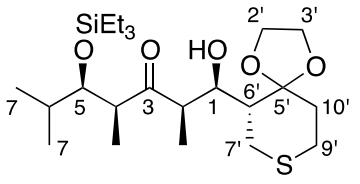
colorless liquid, TLC R_f = 0.43 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3498, 1711 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.72 (1H, br d, *J* = 8 Hz, HC-1), 4.05-3.96 (4H, m, H_2C-2' & H_2C-3'), 3.93 (1H, br s, HO), 3.74 (1H, dd, *J* = 3, 7.5 Hz, HC-5), 3.11 (1H, dq, *J* = 8, 7 Hz, HC-4), 2.94 (1H, dd, *J* = 2.5, 14 Hz, HC-7'), 2.84 (1H, ddd, *J* = 3, 9.5, 13.5 Hz, HC-9'), 2.75-2.62 (2H, m, HC-2 & HC-9'), 2.58 (1H, ddd, *J* = 1.5, 6, 14 Hz, HC-7'), 2.21 (1H, ddd, *J* = 4, 10, 13.5 Hz, HC-10'), 1.94 (1H, m, *J* = 3, 6.5, 8.5 Hz, HC-6'), 1.87 (1H, ddd, *J* = 3.5, 6.5, 13.5 Hz, HC-10'), 1.50 (1H, dqq, *J* = 3, 7, 7 Hz, HC-6), 1.13 (3H, d, *J* = 7 Hz, H_3CC-4), 1.04 (3H, d, *J* = 7 Hz, H_3CC-2), 0.97 (9H, t, *J* = 8 Hz, CH_2CSi ×3), 0.92 (3H, d, *J* = 7 Hz, H_3C-7), 0.87 (3H, d, *J* = 7 Hz, H_3C-7), 0.63 (6H, ap q, *J* = 8 Hz, CH_2Si ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.6 (s, C-3), 110.7 (s, C-5'), 79.7 (d, C-5), 69.7 (d, C-1), 65.1 (t, C-2'), 64.3 (t, C-3'), 48.6 (d, C-2), 47.3 (d, C-4), 45.9 (d, C-6'), 34.2 (t, C-10'), 32.8 (d, C-6), 29.5 (t, C-7'), 27.0 (t, C-9'), 20.6 (q, C-7), 16.8 (q, C-7), 14.6 (q, CH_2C-4), 7.3 (q ×3, CH_2CSi), 7.2 (q, CH_2C-2), 5.7 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{23}H_{44}O_5SSi+Na^+$ 483.2571, found 483.2555 (ESI).



(117ssa)

(1*R*,2*R*,4*S*,5*R*)-*rel*-1-Hydroxy-2,4,6-trimethyl-1-((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)heptan-3-one (117ssa).

Isomerization of **117sss** (55 mg, 0.12 mmol) with *i*-PrMgBr according to the general procedure (*i*-PrMgBr, 3 d) gave a crude product whose ^{1}H NMR spectrum indicated the presence of a 1.5:1 mixture of **117ssa** and **117asa**, respectively. Fractionation of the crude product by FCC (5-10% acetone in pentane) provided **117asa** (14 mg, 25%), a 1.5:1 mixture of **117asa** and **117ssa**, respectively (6 mg, 11%), and the title compound (25 mg, 45%).

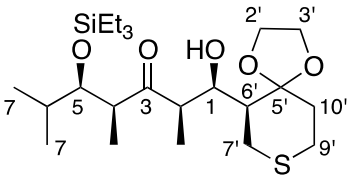
colorless liquid, TLC R_f = 0.43 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3502, 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (1H, br d, *J* = 9 Hz, HC-1), 4.04-3.97 (4H, m, H_2C-2' & H_2C-3'), 3.93 (1H, dd, *J* = 2.5, 8 Hz, HC-5), 3.89 (1H, br s, HO), 3.05 (1H, dq, *J* = 8, 7 Hz, HC-4), 2.91 (1H, dd, *J* = 2.5, 14 Hz, HC-7'), 2.81 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-9'), 2.78 (1H, br q, *J* = 7 Hz, HC-2), 2.75-2.67 (1H, m, HC-9'), 2.59 (1H, ddd, *J* = 1, 6, 14 Hz, HC-7'), 2.18 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10'), 1.95 (1H, ddd, *J* = 3, 6, 9 Hz, HC-6'), 1.85 (1H, ddd, *J* = 3.5, 6, 13.5 Hz, HC-10'), 1.69 (1H, dqq, *J* = 2.5, 7, 7 Hz, HC-6), 1.12 (3H, d, *J* = 7 Hz, H_3CC-4), 1.05 (3H, d, *J* = 7 Hz, H_3CC-2), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.91 (3H, d, *J* = 7 Hz, H_3C-7), 0.86 (3H, d, *J* = 7 Hz, H_3C-7), 0.64 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9 (s, C-3), 110.7 (s, C-5'), 77.6 (d, C-5), 69.5 (d, C-1), 65.0 (t, C-2'), 64.3 (t, C-3'), 47.5 (d, C-4), 46.3 (d, C-2), 46.1 (d, C-6'), 34.3 (t, C-10'), 32.1 (d, C-6), 29.4 (t, C-7'), 27.0 (t, C-9'), 21.1 (q, C-7), 16.2 (q, C-7), 15.6 (q, CH_2C-4), 7.6 (q, CH_2C-2), 7.4 (q ×3, CH_2CSi), 5.7 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{23}H_{44}O_5SSi+Na^+$ 483.2571, found 483.2563 (ESI).



(117sss)

***R*,2*R*,4*S*,5*R*)-*rel*-1-Hydroxy-2,4,6-trimethyl-1-((*S*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)-5-((triethylsilyl)oxy)heptan-3-one (117sss).**

Freshly prepared LiHMDS (0.60 M in THF; 2.0 mL, 1.2 mmol) was added via syringe to a stirring solution of **105** (300 mg, 1.1 mmol) in dry THF (4.0 mL) at –50 °C under argon. After 1.5 h, freshly prepared TiCl(O*i*-Pr)$_3$ (1.6 M in THF; 1.5 mL, 2.4 mmol) was added and the mixture became bright greenish yellow in color. After 1 h, the solution was cooled to –78 °C and a solution **29a** (0.62 g, 3.3 mmol) in THF (2.0 mL) was added. After 3 h (the mixture became lighter in color as the reaction progressed), the reaction was quenched by addition of saturated aqueous NH_4Cl (6 mL). The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were passed over a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and concentrated to give the rude product whose ^{1}H NMR spectrum indicated the presence of **117sss** (dr >10:1 dr) and **29a**. Fractionation of the crude product by FCC (20% ethyl acetate in hexanes) provided **29a** (196 mg, 31%) and the titled compound (406 mg, 80%).

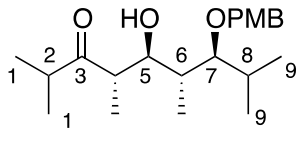
colorless liquid, TLC R_f = 0.34 (20% ethyl acetate in hexanes).

IR (DRIFT) ν_{max} 3519, 1702 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.36 (1H, br dd, *J* = 4, 6.5 Hz, HC-1), 4.06-3.93 (4H, m, H_2C-2' & H_2C-3'), 3.70 (1H, dd, *J* = 3.5, 7 Hz, HC-5), 3.17 (1H, d, *J* = 1.5 Hz, HO), 3.01 (1H, dq, *J* = 6.5, 7 Hz, HC-2), 2.96 (1H, dd, *J* = 10, 14 Hz, HC-7'), 2.85 (1H, dq, *J* = 7, 7 Hz, HC-4), 2.76-2.72 (2H, m, HC-7' & HC-9'), 2.59-2.57 (1H, m, HC-9'), 2.06 (1H, ddd, *J* = 3, 6, 13.5 Hz, HC-10'), 1.98 (1H, ddd, *J* = 3.5, 4, 10 Hz, HC-6'), 1.71 (1H, ddd, *J* = 3.5, 11, 13.5 Hz, HC-10'), 1.62 (1H, dqq, *J* = 3.5, 7, 7 Hz, HC-6), 1.20 (3H, d, *J* = 7 Hz, H_3CC-2), 1.12 (3H, d, *J* = 7 Hz, H_3CC-4), 0.97 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.92 (3H, d, *J* = 7 Hz, H_3C-7), 0.87 (3H, d, *J* = 7 Hz, H_3C-7), 0.63 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.2 (s, C-3), 109.9 (s, C-5'), 78.5 (d, C-5), 68.5 (d, C-1), 64.6 (t, C-2'), 64.5 (t, C-3'), 49.9 (d, C-2), 49.8 (d, C-4), 47.0 (d, C-6'), 35.7 (t, C-10'), 32.8 (d, C-6), 27.4 (t, C-7'), 26.8 (t, C-9'), 20.8 (q, C-7), 16.8 (q, C-7), 14.9 (q, CH_2C-4), 12.3 (q, CH_2C-2), 7.3 (q ×3, CH_2CSi), 5.6 (t ×3, CH_2Si).

HRMS *m/z* calcd for $C_{23}H_{44}O_5SSi+Na^+$ 483.2571, found 483.2571 (ESI).



(127aaa)

(4*S*,5*S*,6*R*,7*S*)-*rel*-7-((4-Methoxyphenyl)methoxy)-5-hydroxy-2,4,6,8-tetramethylnonan-3-one (127aaa).

Isomerization of **127asa**[85] (20 mg, 0.060 mmol) for 1 d according to the general procedure (*i*-PrMgBr) gave a crude product that was a 37:26:19:18 mixture of **127asa**, **127aaa**, **127saa**, and **127ssa**, respectively (14 mg, 70%), by ^{1}H NMR. Fractionation of the mixture by PTLC (10% diethyl ether in dichloromethane) provided **127asa** (5 mg, 25%), a 1:1 mixture of **127saa** and **127ssa** (5 mg, 25%) and the title compound (4 mg, 20%).

colorless liquid, TLC R_f = 0.32 (10% ethyl acetate in hexanes).

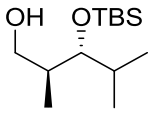
IR (DRIFT) ν_{max} 3479, 1708 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (2H, ap d, *J* = 9.5 Hz, ArH), 6.87 (2H, ap d, *J* = 9.5 Hz, ArH), 4.55 (1H, d, *J* = 11 Hz, OCHAr), 4.50 (1H, d, *J* = 11 Hz, OCHAr), 3.80 (3H, s, H_3CO), 3.65 (1H, ddd, *J* = 5.5, 6, 7 Hz, HC-5), 3.60 (1H, d, *J* = 7 Hz, HO), 3.32 (1H, dd, *J* = 5, 6 Hz, HC-7), 3.05 (1H, dq, *J* = 5.5, 7 Hz, HC-4), 2.64 (1H, ap septet, *J* = 7, 7 Hz, HC-2), 2.00-1.91 (2H, m, HC-6, HC-8), 1.15 (3H, d, *J* = 7 Hz, H_3CC-4), 1.01 (6H, ap d, *J* = 7 Hz, H_3C-1, H_3C-9), 0.98 (6H, ap d, *J* = 7 Hz, H_3C-1, H_3C-9), 0.93 (3H, d, *J* = 7 Hz, H_3CC-6).

^{13}C NMR (150 MHz, $CDCl_3$) δ 221.0 (s, C-3), 159.3 (s, Ar), 131.2 (s, Ar), 129.3 (d ×2, Ar), 113.9 (d ×2, Ar), 87.3 (d, C-7), 78.0 (d, C-5), 74.1 (t, CH_2O), 55.5 (q, CH_3O), 47.3 (d, C-4), 40.8 (d, C-

2), 38.9 (d, C-6), 31.1 (d, C-8), 20.9 (q, C-9), 18.4 (q, C-9 or C-1), 18.3 (q, C-1 or C-9), 18.1 (q, C-1 or C-9), 15.9 (q, CH_3C-6), 15.3 (q, CH_3C-4).

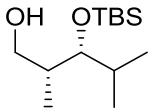
HRMS *m/z* calcd for $C_{21}H_{34}O_4$+Na^+ 373.2349, found 373.2344 (ESI).



(133a)

(2*S*,3*R*)-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (133a).

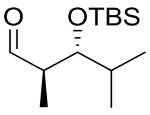
Et_3N (1.80 mL, 1.31 g, 12.9 mmol) and (*c*-Hex)$_2$BCl (1.0 M in hexanes; 11.2 mL, 11.2 mmol) were sequentially added via syringe to a stirring solution of ethyl propionate (1.00 mL, 0.88 g, 8.62 mmol) in Et_2O (26.0 mL) at −78 °C under argon. After 2 h, the mixture was cooled to –95 °C (toluene, liquid N_2) and *i*-PrCHO (1.6 mL, 1.24 g, 17.2 mmol) was added via syringe. After 2 h, the reaction was worked up according to the general procedure. The ^{1}H NMR analysis of the crude product indicated the presence of a 2:1 mixture of **128a** and **128s**, respectively. Fractionation of the crude product by FCC (5% ethyl acetate in hexanes) provided a 2:1 mixture of **128a** and **128s** (621 mg, 41%). Imidazole (195 mg, 2.86 mmol) and TBSCl (372 mg, 2.47 mmol) were sequentially added to a stirring solution of a 2:1 mixture of **128a** and **128s** (358 mg, 2.05 mmol) in dry DMF (3.0 mL) at room temperature. After 3 d, the mixture was diluted with ethyl acetate, washed sequentially with saturated aq NH_4Cl and brine, dried over Na_2SO_4, and concentrated to give the crude product that was a 2.1:1 mixture of **132a** and **132s** (464 mg) by ^{1}H NMR. According to the procedure reported by Reynolds *et al*.,[154] DIBAL-H (1.0 M in cyclohexane, 3.5 mL, 3.5 mmol) was added to a stirred solution of the above crude product (464 mg) in CH_2Cl_2 (2.8 mL) at −78 °C. After 30 min, the mixture was warmed to 0 °C and the reaction was quenched by addition of MeOH (0.1 mL) and then the mixture was diluted with CH_2Cl_2 followed by addition of satd aq Rochelle's salt. The mixture was stirred at room temperature for 1 h and then the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexanes) to give the title compound (175 mg, 35% over two steps) and **133s** (83 mg, 16% over two steps). The NMR data for **133s** closely matched those previously reported for (−)-**133a**.[176]



(133s)

(2*R*,3*R*)-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (133s).

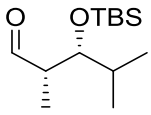
The minor product isolated from the preparation of **133a**. The NMR data for **133s** closely matched those previously reported.[177]



(134a)

(2*R*,3*R*)-*rel*-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylpentanal (134a).

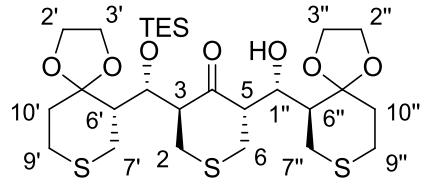
A solution ofd ry DMSO (38 μL, 0.543 mmol) in CH_2Cl_2 (0.30 mL) was added dropwise to a stirring solution of $(COCl)_2$ (24 μL, 0.272 mmol) in CH_2Cl_2 (0.60 mL) at −78 °C under argon. After 15 min, a solution of **133a** (60 mg, 0.247 mmol) in CH_2Cl_2 (0.30 mL) was added. After 15 min, Et_3N (0.17 mL, 1.23 mmol) was added. After 5 min, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 15 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to afford the crude product, **133a** (60 mg, >99% yield, >90% pure) that was used for next step without further purification. The NMR data for **134a** closely matched those previously reported.[178]



(134s)

(2*S*,3*R*)-*rel*-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylpentanal (134s).

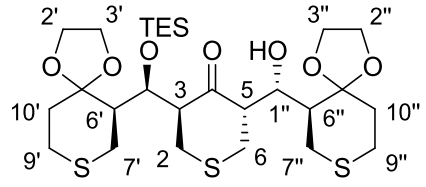
Alcohol **133s** (60 mg, 0.247) was converted to **134s** (59 mg, >99% yield, >95% pure) following the procedure described for **134a**. The NMR data for **134s** closely matched those previously reported.[178]



(144asa)

(3*S*,5*S*)-*rel*-3-[(*R*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (144asa).

According to the general procedure for isomerizations of thiopyranone aldols, the ^{1}H NMR spectrum of the crude product obtained from reaction of **67b** (20 mg, 0.047 mmol) with **29a** (18 mg, 0.09 mmol) indicated the presence of 1:0.09:0.02:0.26 mixture of **144asa**, **144aas**, **144sas** and **67b**. Fractionation of the crude product by FCC (60-80% diethyl ether in hexanes) gave the title compound (22 mg, 76%). The ^{1}H and ^{13}C NMR data for **144asa** closely matched those previously reported.[134]

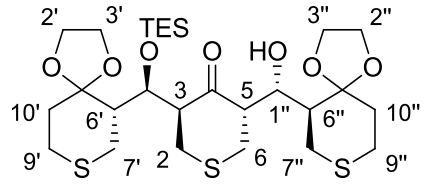


(145asa)

(3*S*,5*S*)-*rel*-3-[(*S*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (145asa).

According to the general procedure for isomerizations of thiopyranone aldols, the ^{1}H NMR spectrum of the crude product obtained from reaction of **66b** (20 mg, 0.047 mmol) with **29a** (18 mg, 0.09 mmol) indicated the presence of 0.91:0.18:0.14:0.1:0.1:0.2 mixture of **145asa**, **145ass**, **145aas**, an unidentified aldol adduct, **145aaa** and **66b**. Fractionation of the crude product by FCC

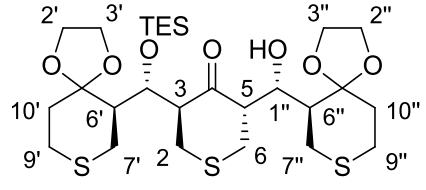
(50-70% diethyl ether in hexanes) gave a 1:0.43:0.33:0.12 mixture of **145ass**, the unidentified aldol adduct, **145aaa**, **145aas** (8 mg, 28%) and 15:1 mixture of the title compound and **145aas** (19 mg, 66%) which was further purified by PTLC (20% *i*-PrOH in hexanes) to afford the title compound (16 mg, 55%) and 2.3:1 mixture of the title compound and **145aas** (3 mg, 11%). The ^{1}H and ^{13}C NMR data for **145asa** closely matched those previously reported.[134]



(146asa)

(3*S*,5*S*)-*rel*-3-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxymethyl)-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (146asa).

According to the general procedure for isomerizations of thiopyranone aldols, the ^{1}H NMR spectrum of the crude product obtained from reaction of **68b** (20 mg, 0.047 mmol) with **29a** (18 mg, 0.09 mmol) indicated the presence of 1.3:0.35:0.23:0.8 mixture of **146asa**, **146sas**, **146aas** and **68b**. Fractionation of the crude product by FCC (50-70% diethyl ether in hexanes) gave recovered **68b** (6 mg, 30%), **146sas** (4 mg, 14%), a 1:0.3:1 mixture of **146asa**, **146sas**, **146aas** (6 mg, 21%), and the title compound (11 mg, 38%). The ^{1}H and ^{13}C NMR data for **146asa** closely matched those previously reported.[134]



(147asa)

(3*S*,5*S*)-*rel*-3-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4H-thiopyran-4-one (147asa)

According to the general procedure for isomerizations of thiopyranone aldols, the ^{1}H NMR spectrum of the crude product obtained from reaction of **69b** (20 mg, 0.047 mmol) with **29a** (18

mg, 0.09 mmol) indicated the presence of a single aldol product (>19:1 dr). Fractionation of the crude product by FCC (60-90% diethyl ether in hexanes) gave the title compound (23 mg, 79%). The ^{1}H and ^{13}C NMR data for **147asa** closely matched those previously reported.[134]

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6. APPENDIX

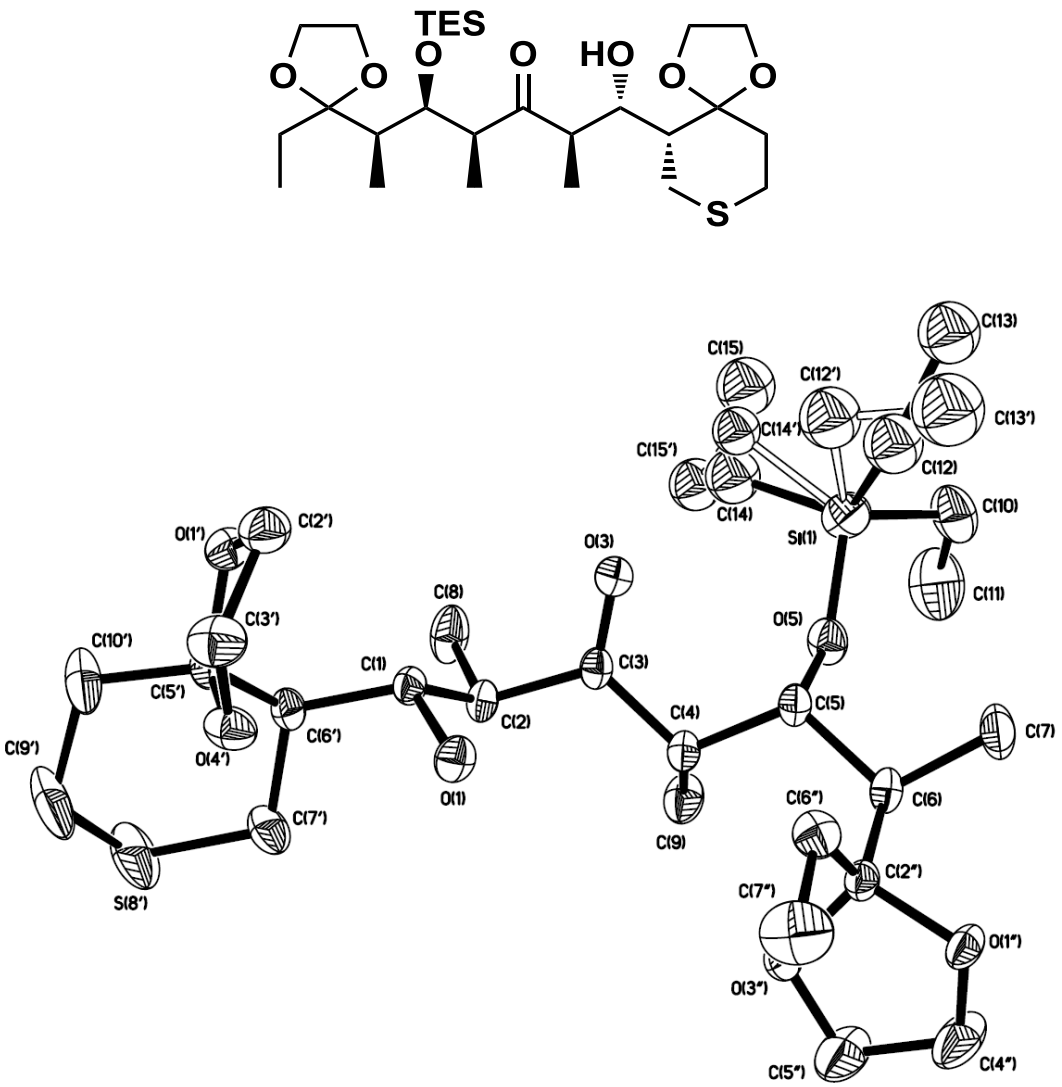

Figure A.1. ORTEP for **74sas**.

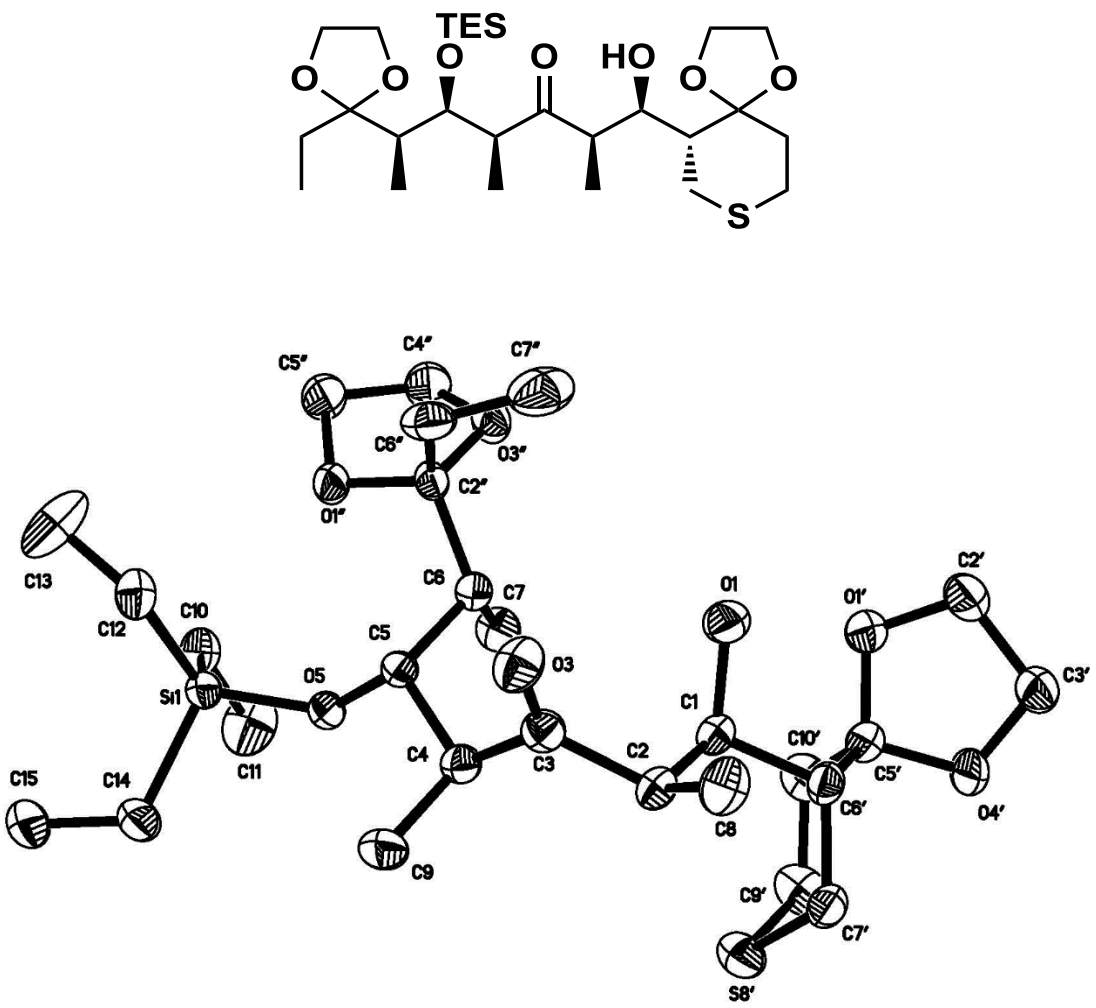

Figure A.2. ORTEP for **74ssa**.

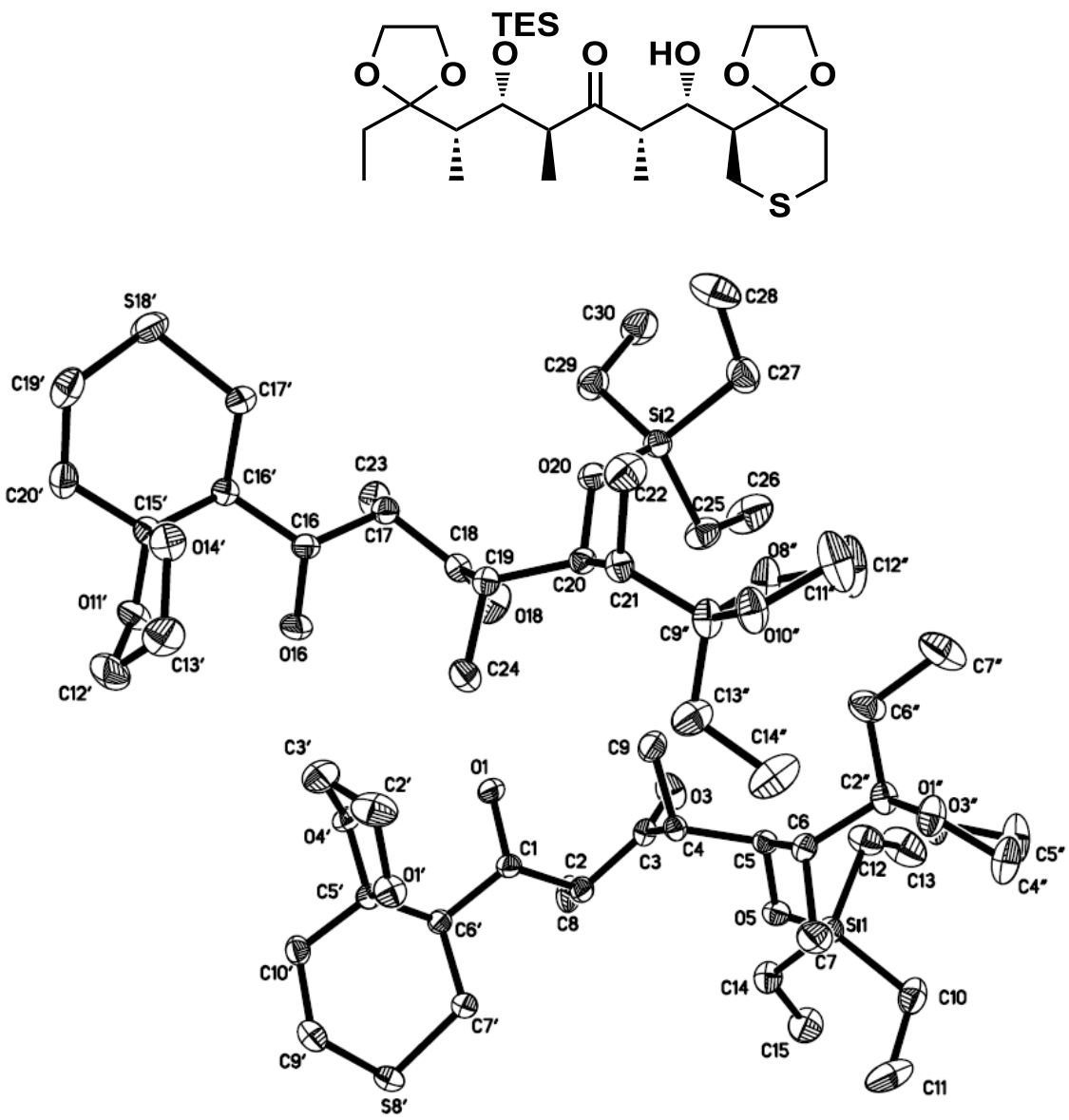

Figure A.3. ORTEP for **75asa**.

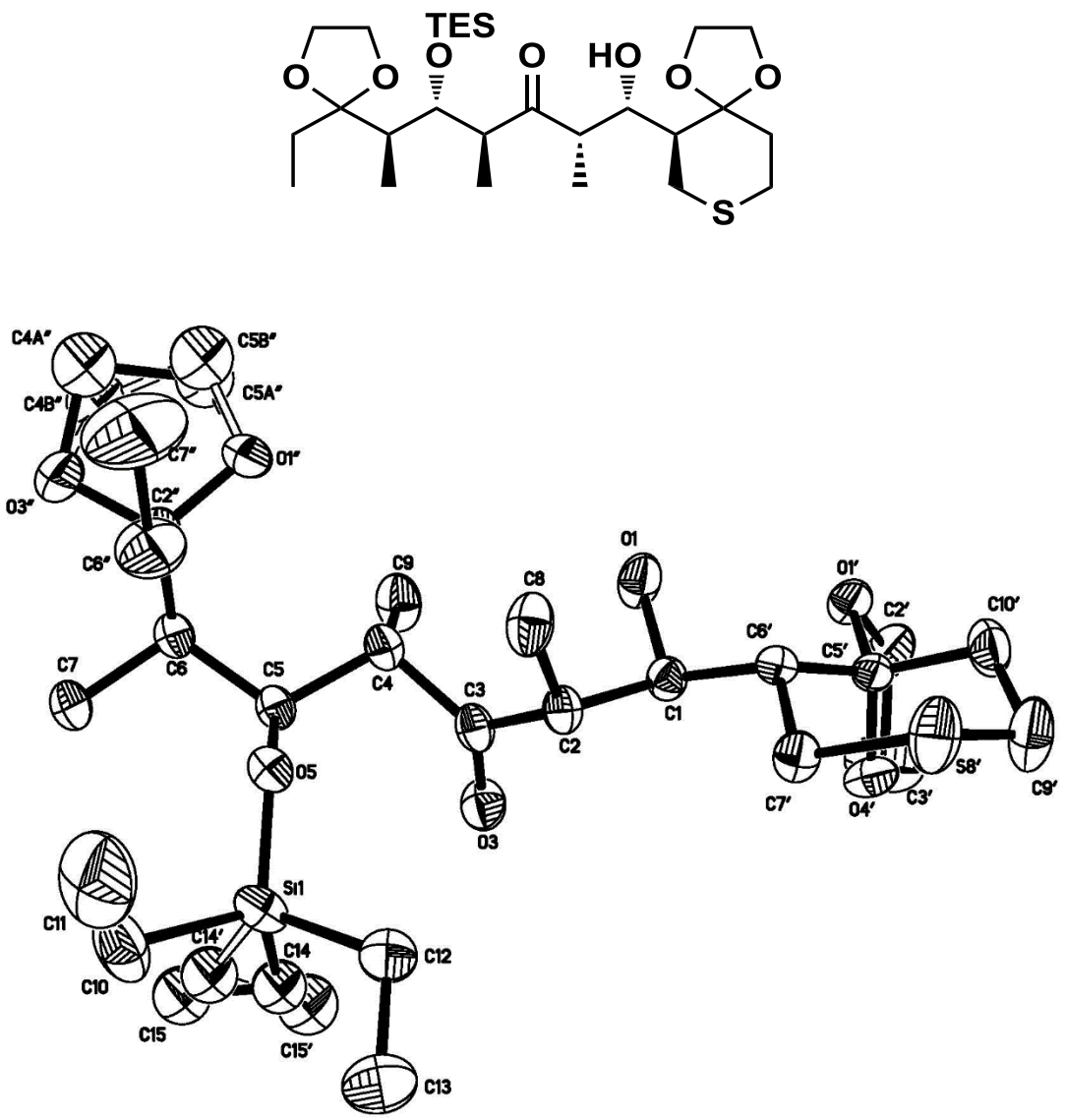

Figure A.4. ORTEP for **77asa**.